

PUBLIC UNIVERSITY OF NAVARRE
DEPARTMENT OF HEALTH SCIENCES



**Prevalence of non-responders to exercise-training
for improving cardiometabolic and performance
outcomes**

Doctoral Thesis

Cristian Alvarez

May 2018

Supervisor: Prof. Mikel Izquierdo,
Co-Supervisors: Prof. Rodrigo Ramírez-Campillo
Prof. Robinson Ramírez-Vélez

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Ph.D. Thesis
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List of Abbreviations by alphabet

Abbreviation	Meaning
AbdSF	Abdominal skinfold
BMI	Body mass index
CT	Concurrent training
DBP	Diastolic blood pressure
ES	Effect size
EM	Early biological maturation
FGL	Fasting glucose
FINS	Fasting insulin
HbA1c	Glycated haemoglobin
HBP	High blood pressure
HOMA-IR	Homeostasis model assessment of insulin resistance
HIT	High-intensity interval training
IR	Insulin resistance
IVRET	Inter-individual variability to exercise training
MET	Basal metabolic equivalent rate
NR	Non-responders
NM	Normal biological maturation
OGTT	Oral glucose tolerance test
OR	Odds ratios
RPE	Rating of perceived exertion
RT	Resistant training
R	Responders
SSF	Subscapular skinfold
SISF	Supra-iliac skinfold
SBP	Systolic blood pressure
TSF	Tricipital skinfold
T2DM	Type 2 Diabetes Mellitus
TE	Technical error
VO ₂ peak	Peak of oxygen uptake
VO ₂ max	Maximum oxygen uptake
WC	Waist circumference
1RM	One-maximum repetition strength test
1RM _{BC}	One-maximum repetition strength test of biceps curl
1RM _{LE}	One-maximum repetition strength test of leg extension
1RM _{SP}	One-maximum repetition strength test of shoulder press
1RM _{UR}	One-maximum repetition strength test of upper row

Abbreviations

2KMWT	2 kilometre walking test
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List of Abbreviations by parameters studied

Body composition abbreviations	
Abbreviation	Meaning
AbdSF	Abdominal skinfold
BMI	Body mass index
SISF	Supra-iliac skinfold
SSF	Subscapular skinfold
TSF	Tricipital skinfold
MET	Metabolic energy equivalents
WC	Waist circumference
EM	Early biological maturation
NM	Normal biological maturation
Cardiovascular abbreviations	
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HRR	Heart rate at rest
HBP	High blood pressure
Metabolic abbreviations	
FGL	Fasting glucose
FINS	Fasting insulin
HbA1c	Glycated haemoglobin
HOMA-IR	Homeostasis model assessment of insulin resistance
IR	Insulin resistance
T2DM	Type 2 Diabetes Mellitus
OGTT	Oral glucose tolerance test
HbA1c	Glycated haemoglobin
Performance abbreviations	
CT	Concurrent training
RT	Resistant training
HIT	High-intensity interval training
RPE	Rate of perceived exertion
VO ₂ peak	Peak of oxygen uptake
VO ₂ max	Maximum oxygen uptake
1RM	One-maximum repetition strength test
1RM _{BC}	One-maximum repetition strength test of biceps curl
1RM _{LE}	One-maximum repetition strength test of leg extension

Abbreviations

1RM _{SP}	One-maximum repetition strength test of shoulder press
1RM _{UR}	One-maximum repetition strength test of upper row
2KMWT	2 kilometre walking test

Statistical abbreviations

ES	Effect size
OR	Odds ratios
TE	Technical error

Other abbreviations

IVRET	Inter-individual variability to exercise training
NR	Non-responders
R	Responders

Declaration

I, Cristian Alvarez, do hereby declare that the research presented in this dissertation is based on 6 articles (chapters 2 to 6) that have been published or accepted/submitted for publication in international peer-reviewed journals. To meet the stylistic requirements of a thesis, the formats of the papers have been adjusted accordingly throughout. These edits did not substantially change the content of the published articles. The role which I fulfilled within each of the publications is presented below.

Chapter 2

Cristian Álvarez, Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez, and Mikel Izquierdo. Effects and prevalence of nonresponders after 12-weeks of high-intensity interval or resistance training in women with insulin resistance: a randomized trial. Journal of applied physiology 2017;(122):985-996. (ISI-WOS, Q1, IF 3.3).

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Chapter 3

Cristian Álvarez, Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez and Mikel Izquierdo. Prevalence of non-responders for glucose control markers after 10-weeks of high-intensity interval training in adult women with higher and lower insulin resistance. Frontiers in physiology 2017;(8):479. (ISI-WOS, Q1, IF 4.1).

This work was supported by the health promotion program of the Public Health Service of Los Ríos government (SSVV). MI was funded by research grants from the Spanish Net on Aging and frailty (RETICEF) (ISCIII, FEDER) and Centro de Investigación Biomédica en Red (CIBER) en Fragilidad y Envejecimiento Saludable (CIBERFES; CB16/10/00315) del Instituto de Salud Carlos III (FEDER).

Chapter 4

Cristian Alvarez, Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez and Mikel Izquierdo. Effects of 6-weeks high-intensity interval training in schoolchildren with insulin resistance: influence of biological maturation on metabolic, body composition,

cardiovascular and performance non-responses. Frontiers in physiology 2017;(8):444. (ISI-WOS, Q1, IF 4.1).

This work was supported by the health promotion program of the Public Health Service of Los Ríos Government (SSVV), by the Family Healthcare Center Tomás Rojas of Los Lagos, and by the Public Hospital of Los Lagos.

Chapter 5

Cristian Álvarez, Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez, Cristian Martínez, Mauricio Castro-Sepúlveda, Alonso Alonso-Martínez and Mikel Izquierdo. *Metabolic effects of resistance or high-intensity interval training among glycaemic control-nonresponsive children with insulin resistance. International journal of obesity 2018;(42)79-87. (ISI-WOS, Q1, IF 5.4).*

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Chapter 6

C. Álvarez, R. Ramírez-Vélez, R. Ramírez-Campillo, I. Shigenori, C. Celis-Morales, A. García-Hermoso, L. Rodríguez-Mañas, A. Lucia, M. Izquierdo. Inter-individual responses to different exercise stimuli among insulin-resistant women. Scandinavian Journal of Medicine and Science in Sports, In Press. *(ISI-WOS, Q1, IF 3.3).*

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Chapter 7

Cristian Álvarez, Rodrigo Ramírez-Campillo, Alejandro Lucía, Robinson Ramírez-Vélez, and Mikel Izquierdo. Concurrent training and prediabetes comorbidities: an analysis of non-responders using clinical cut-off points. Submitted.

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List of publications

Cristian Álvarez, Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez, and Mikel Izquierdo. *Effects and prevalence of nonresponders after 12-weeks of high-intensity interval or resistance training in women with insulin resistance: a randomized trial. Journal of applied physiology* 2017;(122):985-996. (ISI-WOS, Q1, IF 3.3).

Cristian Álvarez, Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez and Mikel Izquierdo. *Prevalence of non-responders for glucose control markers after 10-weeks of high-intensity interval training in adult women with higher and lower insulin resistance. Frontiers in physiology* 2017;(8):479. (ISI-WOS, Q1, IF 4.1).

Cristian Alvarez, Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez and Mikel Izquierdo. *Effects of 6-weeks high-intensity interval training in schoolchildren with insulin resistance: influence of biological maturation on metabolic, body composition, cardiovascular and performance non-responses. Frontiers in physiology* 2017;(8):444. (ISI-WOS, Q1, IF 4.1).

Cristian Álvarez, Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez, Cristian Martínez, Mauricio Castro-Sepúlveda, Alonso Alonso-Martínez and Mikel Izquierdo. *Metabolic effects of resistance or high-intensity interval training among glycemic control-nonresponsive children with insulin resistance. International journal of obesity* 2018, (42)79-87. (ISI-WOS, Q1, IF 5.4).

Cristian Álvarez, R. Ramírez-Vélez, R. Ramírez-Campillo, S. Ito, C. Celis-Morales, A. García-Hermoso, L. Rodríguez-Mañas, A. Lucia, M. Izquierdo. *Inter-individual responses to different exercise stimuli among insulin-resistant women. Scandinavian Journal of Medicine and Science in Sports, In Press.* (ISI-WOS, Q1, IF 3.3).

Cristian Álvarez, Rodrigo Ramírez-Campillo, Alejandro Lucía, Robinson Ramírez-Vélez, and Mikel Izquierdo. *Concurrent training and prediabetes comorbidities: an analysis of non-responders using clinical cutoff points. Submitted.*

Conference Papers

Alvarez C, Ramírez-Vélez R, Ramírez-Campillo R, Shigenori I, Celis-Morales C, García-Hermoso A, Rodríguez-Mañas L, Lucia A and Izquierdo M. Inter-individual responses to different exercise stimuli among insulin-resistant adult women: using the no-response for choosing exercise programs. ***Primera jornada de investigación e innovación en salud: actividad física, gestión del cuidado y rehabilitación.***

Oral communication by Alvarez C, 9th and 10th November 2017, Talca, Chile

Alvarez C, Ramírez-Vélez R, Ramírez-Campillo R, Shigenori I, Celis-Morales C, García-Hermoso A, Rodríguez-Mañas L, Lucia A and Izquierdo M. Inter-individual responses to different exercise stimuli among insulin-resistant adult women: using the no-response for choosing exercise programs. ***VIII seminario internacional III congreso nacional de ciencia de la actividad física y del deporte.***

Oral communication by Alvarez C, 15th and 16th november 2017, Concepción, Chile.

Alvarez C, Ramírez-Vélez R, Ramírez-Campillo R, Shigenori I, Celis-Morales C, García-Hermoso A, Rodríguez-Mañas L, Lucia A and Izquierdo M. Inter-individual responses to different exercise stimuli among insulin-resistant adult women: using the no-response for choosing exercise programs. ***XVI seminario nacional y VI seminario de investigación en ciencias de la actividad física, didáctica de la educación física y estilos de vida saludable.***

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“1000 gracias de corazón, a todos los que me ayudaron en este proceso, y no duden que haré menos por todos los pares quienes vienen y estar por venir”.

“1000 thanks from my heart, to all those who help me in this process, and there is no doubt that I’ll do the same with all our peers who are below of us”

Summary / Resumen

Summary (English)

Resumen (Español)

Global summary of the 6 studies

The current PhD dissertation described how the regular and beneficial reported results in 'mean' terms from some exercise training modes such as resistant training (RT), high-intensity interval training (HIT) or concurrent training (CT), can promote at inter-individual level some subjects/participants who respond (R) and do not respond (i.e., subjects who do not change, or that show a worsened response after exercise training) to improve cardiometabolic/performance outcomes, considered non-responders (NR) according to some unexplored environmental/endogenous factors such as a) mode of training, b) a high- low-degree level of metabolic disease named as 'health status', c) different sexual biological maturation, or d) according with different criteria for NR classification. This doctoral thesis is based on 6 scientific studies that have been published and accepted/submitted for publication in a scientific international journal.

The main results of our 6 studies are expressed according with their aims as follow; study 1 (chapter 2) to investigate the effects and prevalence of NR to HIT and RT in adult woman with insulin resistance (IR) on glucose control parameters, where we concluded that; twelve-weeks of HIT and RT have similar effects and NR prevalence to improve glucose control variables; however, there is different NR prevalence in other anthropometric, cardiovascular, strength and endurance performance measurements in insulin resistance adult woman. Study 2 (chapter 3) to assess the effects of HIT and the prevalence of NR in adult women with higher and lower levels of IR, where we concluded that; independent of the 'magnitude' of the cardiometabolic disease, there is no difference in the NR prevalence with regard to improved homeostasis model assessment of IR (HOMA-IR) or to body composition, cardiovascular, and muscle performance co-variables after 10-weeks of HIT in sedentary adult women. Study 3 (chapter 4) to compare the effects and prevalence of NR to improve the IR level, as well as to other body composition, cardiovascular, and performance co-variables, between early (EM) and normal maturation (NM) in insulin resistance (IR) schoolchildren after 6-weeks of HIT, where we concluded that, although there were no differences in the prevalence of NR to metabolic variables between groups of IR schoolchildren of different maturation starting, other differences were found to body mass and systolic blood pressure (SBP), suggesting that body composition and cardiovascular parameters can be playing a role in the NR prevalence after HIT. In the study 4 (chapter 5) we aimed to investigate which among 20-cardiometabolic and performance outcomes do and do not respond to HIT, RT, or CT in insulin-resistant adult women, to report both training-induced changes and the prevalence of NR, where we concluded that independent of the mode of training including volume and frequency, RT has an important ability to reduce the prevalence of non-response to improve the

20-outcomes of health and performance in IR adult women. Study 6 (chapter 7) with aim of examining 'mediators' to the effects of 6-weeks of RT or HIT on glucose control parameters in physically inactive schoolchildren with IR, and to determine both training-induced changes and the prevalence of NR to decrease the IR level, where or main conclusions were that; the improvements in the lower body strength and the decreases in waist circumference can explain more the effects of the improvements in glucose control of IR schoolchildren in responders (R) group after 6-weeks of RT or HIT, and finally, in the study 6 (chapter 7), the aims were to investigate the effects of a 20-week CT intervention on cardiovascular risk factors such as body composition, blood pressure and lipid profile among adult women with hyperglycemia and to report the prevalence of NR for the different study outcomes, being concluded that; in addition to its benefits on glucose homeostasis, a 20-weeks CT intervention for women with prediabetes can decrease abdominal obesity and improve lipid profile in 'mean' terms, as well as enhance the clinical status of some individuals (i.e., those who are responders) from a 'high' to a 'normal'/'low' cardiovascular risk after training.

In brief, the main conclusions of this thesis, and according to each study are that a) HIT and RT show similar effects and NR prevalence to improve glucose control in IR adult woman, b) independent of the 'magnitude' of the glucose control degree, there are similar NR prevalence to improve HOMA-IR, c) there were no differences in the prevalence of NR to metabolic variables between IR schoolchildren of different biological maturation starting but not to other health-related and performance outcomes, d) the improvements in the strength performance and the decreases in waist circumference can explain more the effects of the glucose control improvements of IR schoolchildren, e) independent of the mode of training including volume and frequency, RT has an important ability to reduce the prevalence of NR to improve the 20-outcomes of health and performance in IR adult women and f) a CT intervention for women with prediabetes report both R and NR for a change of the altered clinical status of some individuals using two different NR criteria classification.

Study 1 (Chapter 2)

Background/aims: Our aim was to investigate the effects and prevalence of NR to HIT and RT in adult woman with IR on glucose control parameters. **Methods:** Sedentary overweight/obese insulin resistant adult women (age = 33.5 ± 6.5 years; BMI = 29.9 ± 3.7 kg/m²) were randomly assigned to a tri-weekly HIT program (HIT; $N = 20$) or resistant training (RT; $N = 20$). Glucose control fasting glucose, fasting insulin and HOMA-IR, as well as additional body composition, cardiovascular, and muscle, and endurance performance co-variables were measured before and after 12-weeks in both intervention groups. **Results:** Improvements ($P < 0.05$) in the fasting glucose (-6.6% and

-5.8%), fasting insulin (-47.2% and -38.1%), and HOMA-IR (-50.0% and -36.3%) were identified to HIT and RT group, respectively after training. There were no differences in the NR prevalence between HIT and RT for decreasing fasting glucose (16.6 vs. 29.4%, OR = 1.9; 95%CI 0.4, 10.5), fasting insulin (11.1 vs. 11.7%, OR = 1.0; 95%CI 0.1, 8.5), and HOMA-IR 11.1 vs. 11.7%, OR = 1.7; 95%CI 0.2, 11.7) respectively to each group, after intervention; however, there were significant differences in the NR prevalence in other anthropometric (body mass, BMI, tricipital skinfold, fat, and muscle mass), cardiovascular (heart rate at rest, diastolic blood pressure), and performance co-variables included ($1RM_{BC}$, $1RM_{LE}$, $1RM_{SP}$, $1RM_{UR}$) after intervention. **Conclusions:** 12-weeks of HIT and RT have similar effects and NR prevalence to improve glucose control variables; however, there is different NR prevalence in other body composition, cardiovascular, strength and endurance performance measurements in IR adult woman. These findings were displayed with a similar time investment/week of 114 vs. 108 min, respectively to HIT and RT.

Study 2 (Chapter 3)

Background/aims: Exercise training improves performance and biochemical parameters on average, but wide inter-individual variability exists. This study assessed the effects of HIT and the prevalence of NR in adult women with higher and lower levels of IR. **Methods:** Forty adult women were assigned to a HIT program, and after training were analysed in two groups; a group with higher IR (H-IR, 40 \pm 6 years; BMI: 29.5 \pm 3.7 kg/m²; N = 20) and a group with lower IR (L-IR, 35 \pm 9 years; 27.8 \pm 2.8 kg/m²; N = 20). Body composition, cardiovascular, metabolic and performance variables were measured at baseline and after 10-weeks of training. **Results:** There were significant training-induced changes [delta percent (1%)] in fasting glucose, fasting insulin, and HOMA-IR scores in the H-IR group (-8.8, -26.5, -32.1%, P <0.0001), whereas no significant changes were observed in the L-IR. Both groups showed significant pre-post changes in other body composition variables [waist circumference (-5.2, P <0.010, and -3.8%, P =0.046) and tricipital (-13.3, P <0.010, and -13.6%, P <0.0001), supra-iliac (-19.4, P <0.0001, and -13.6%, P <0.0001), and abdominal (-18.2, P <0.0001, and -15.6%, P <0.010) skinfold measurements]. SBP decreased significantly only in the L-IR group (-3.2%, P <0.010). Both groups showed significant increases in one maximum repetition test of leg-extension [$1RM_{LE}$] (+12.9, P <0.010, and +14.7%, P =0.045). There were significant differences in the prevalence of NR between the H-IR and L-IR groups for fasting glucose (25 vs. 95%, P <0.0001) and fasting insulin (P =0.025). **Conclusions:** Independent of the 'magnitude' of the cardiometabolic disease, no differences were observed in the NR prevalence with regard to improved HOMA-IR or to body composition, cardiovascular, and muscle performance co-variables after 10-weeks of HIT in sedentary IR adult women.

Study 3 (Chapter 4)

Background/aims: Previous studies have observed significant heterogeneity in the magnitude of change in measures of metabolic response to exercise training. The aim of this study was to compare the effects and prevalence of NR to improve the IR level, as well as to other body composition, cardiovascular, and performance co-variables, between early (EM) and normal maturation (NM) in IR schoolchildren after 6-weeks of HIT. **Methods:** Sedentary children (age 11.4 ± 1.7 years) were randomized to either HIT-EM group ($N = 12$) or HIT-NM group ($N = 17$). Fasting glucose (FGL), fasting insulin (FINS) and HOMA-IR were assessed as the main outcomes. **Results:** There were no significant differences between groups in the prevalence of NR based on FGL, FINS, and HOMA-IR. There were significant differences in NR prevalence to decrease co-variables body mass (HIT-EM 66.6% vs. HIT-NM 35.2%) and SBP (HIT-EM 41.6% vs. HIT-NM 70.5%). A high risk [based on odds ratios (OR)] of NR cases was detected for FGL, OR = 3.2 (0.2 to 5.6), and HOMA-IR, OR = 3.2 (0.2 to 6.0). Additionally, both HIT-EM and HIT-NM groups showed significant decreases. ($P < 0.05$) in TSF, SSF, and AbdSF skinfold, and similar decreases in fasting insulin and HOMA-IR. The HIT-EM group showed significant decreases in SBP. The HIT-NM group showed significant increases in $1RM_{LE}$ and $1RM_{UR}$. **Conclusions:** Although there were no differences in the prevalence of NR to metabolic variables between groups of IR schoolchildren of different maturation starting, other differences were found to body mass and SBP, suggesting that body composition and cardiovascular parameters can be playing a role in the NR prevalence after HIT. These results were displayed with several metabolic, body composition, blood pressure, and performance improvements independent of an early/normal maturation or the prevalence of NR.

Study 4 (Chapter 5)

Background/aims: Little evidence exists on which variables of body composition or muscular strength mediates more glucose control improvements and the prevalence of NR in children. We examined 'mediators' to the effects of 6-weeks of RT or HIT on glucose control parameters in physically inactive schoolchildren with IR. Secondly, we also determined both training-induced changes and the prevalence of NR to decrease the IR level. **Methods:** Fifty-six children diagnosed with IR followed a RT or supervised HIT program for 6-weeks. Participants were classified based on Δ HOMA-IR into glycaemic control R (decrease in homeostasis model assessment-IR (HOMA-IR) ≤ 3.0 after intervention) and NR (no changes or values HOMA-IR ≥ 3.0 after intervention). The primary outcome was HOMA-IR associated with their mediators. **Results:** Mediation analysis revealed that improvements (decreases) in waist circumference could explain more the effects (decreases) of HOMA-IR. **Conclusions:** The

improvements in the lower body strength and the decreases in waist circumference can explain more the effects of the improvements in glucose control of IR schoolchildren in R group after 6-weeks of RT or HIT, showing both regimes similar effects on body composition or muscular strength independent of inter-individual metabolic response variability.

Study 5 [Accepted] (Chapter 6)

Background/aims: To investigate which among 20-cardiometabolic and performance outcomes do and do not respond to HIT, RT or CT in IR adult women. A secondary aim was to report the training-induced changes and the prevalence of non-responders.

Methods: Forty-five IR adult women were randomly assigned to one of the following four groups: HIT (39.2 ± 9.5 y; body mass index [BMI], 29.3 ± 3.3 , $N = 14$), RT (33.9 ± 9.3 y; BMI, 29.4 ± 5.5 ; $N = 8$), CT (43.3 ± 8.1 y; BMI, 29.1 ± 2.9 ; $N = 10$), and a control group (CG, 40.1 ± 11.4 y; BMI, 28.3 ± 3.5 ; $N = 13$). 9-body composition, 3-cardiovascular, 3-metabolic, and 5-performance outcomes were assessed at baseline and after 12-weeks of intervention. **Results:** Considering all outcomes, the lowest number of total non-responses for one or more variables was found in the RT group, followed by the CT and HIT groups. Individuals in the CG group were classified as NR for almost all the variables. Moreover, there were several significant changes in body composition and metabolic parameters, including fasting glucose (HIT: -5.7, RT -5.1 mg/d); fasting insulin (HIT: -0.6, RT -0.6 μ IU/mL) and HOMA-IR (HIT: -0.3, RT -0.4), in addition to improvements in cardiovascular and performance parameters. Also, there were significant differences among groups in the prevalence of NR for the variables where a non-response was detected. **Conclusions:** Overall, the study suggests that independent of the mode of training including volume and frequency, RT has an important ability to reduce the prevalence of non-response to improve the 20-outcomes of health and performance in IR adult women.

Study 6 [Submitted] (Chapter 7)

Background/aims: To investigate the effects of a 20-weeks CT intervention on cardiovascular risk factors such as body composition, blood pressure and lipid profile among adult women with hyperglycemia. A secondary aim was to report prevalence of NR for the different study outcomes. **Methods:** Physically inactive overweight/obese and hyperglycemic adult women (age = 42 ± 6 years; BMI = 30.9 ± 4.8 kg/m²) were randomly assigned to a 20-week CT intervention group or a control (non-exercise) group (CG), ($N = 14$ /group). Comorbidities indices for body composition, blood pressure and metabolic were assessed before and after the 20-weeks intervention.

Results: Beyond a decrease in fasting glucose (-4 mg/dL on average, $P = 0.05$),

significant benefits of CT were found for mean values in adiposity (body mass -1.3 kg, $P = 0.026$ and WC -4.0 cm, $P < 0.0001$) and lipid profile (total cholesterol -12 mg/dL, $P = 0.038$; LDL-cholesterol -11 mg/dL, $P = 0.022$; HDL-cholesterol +4 mg/dL, $P = 0.003$; and triglycerides -25 mg/dL, $P < 0.0001$), were these outcomes do not showed changed in control group. At the individual level, the proportion of R and NR were the following: for WC (CT 14% and 86%; CG 0% and 100%), for SBP (CT 36% and 14.2%; CG 14% and 7%), for diastolic blood pressure [DBP] (CT 0% and 0%; CG 7% and 14%), for total- (CT 14% and 29%; CG 7% and 28%), LDL- (CT 21% and 36%; CG 0% and 43%), HDL-cholesterol (CT 14% and 50%; CG 14% and 57%) and triglycerides (CT 21% and 14%; CG 0% and 43%), respectively. **Conclusions:** In addition to its benefits on glucose homeostasis, a 20-weeks CT intervention for women with prediabetes can decrease abdominal obesity and improve lipid profile in 'mean' terms, as well as enhance the clinical status of some individuals (*i.e.*, those who are R) from a 'high' to a 'normal'/'low' cardiovascular risk after training.

Resumen global de los 6 estudios

La presente tesis doctoral describe cómo los benéficos y regulares efectos de algunos modos de ejercicio físico tales como el ejercicio de fuerza (RT), el ejercicio intermitente de alta intensidad (HIT), o el ejercicio combinado (CT), pueden promover también a nivel inter-individual que algunos sujetos respondan (R) y que también no respondan para mejorar (i.e., sujetos quienes no cambian, o que muestran un empeoramiento en una variable) parámetros cardiometabólicos/performance, siendo considerados como no-respondedores (NR), de acuerdo a algunos no explorados factores ambientales/endógenos así como a) el modo de ejercicio, b) el grado de enfermedad (i.e., un elevado/bajo nivel de enfermedad cardiometabólica), c) la edad de maduración biológica, o d) de acuerdo al criterio técnico de clasificación de NR. Esta tesis doctoral está basada en 6 estudios científicos que han sido publicados o aceptados/enviados en revistas científicas internacionales.

Los mayores hallazgos de nuestros 6 estudios son expresados de acuerdo con sus siguientes y respectivos objetivos de cada estudio; estudio 1 (capítulo 2) investigar los efectos y la prevalencia de NR para el ejercicio HIT y el ejercicio de RT en mujeres adultas con IR sobre parámetros de control glicémico, donde nosotros concluimos que; doce semanas de HIT o RT tienen similares efectos y prevalencia de NR para mejorar variables de control glicémico; sin embargo, existe una diferente prevalencia de NR en otras variables de composición corporal, cardiovasculares, de la performance endurance y de fuerza medidas en mujeres adultas con IR. Estudio 2 (capítulo 3) para medir los efectos del ejercicio HIT y la prevalencia de NR en mujeres adultas elevados y bajos niveles de IR, donde nosotros concluimos que; independiente de la ‘magnitud’ de una enfermedad cardiometabólica, no existen diferencias en la prevalencia de NR con respecto a mejorar el HOMA-IR o variables de composición corporal, cardiovasculares y performance de fuerza después de 10 semanas de HIT en mujeres adultas sedentarias con IR. Estudio 3 (capítulo 4) comprar los efectos y prevalencia de NR para mejorar los niveles de IR, así como otras co-variables de composición corporal, cardiovasculares y de performance entre niños escolares con IR de temprana (EM) o normal (NM) maduración biológica después de 6 semanas de HIT, donde nosotros concluimos que, aunque no existieron diferencias en la prevalencia de NR para variables metabólicas ente grupos, otras diferencias fueron detectadas en la prevalencia de NR para mejorar variables como el peso corporal y la presión sistólica, sugiriéndose que una temprana o normal maduración biológica podrían estar jugando un rol en la prevalencia de NR después de HIT. Estudio 4 (capítulo 5) con el objetivo de examinar los ‘mediadores’ de los efectos de 6 semanas de ejercicio de RT o ejercicio HIT sobre parámetros de control glicémico en niños escolares con IR físicamente inactivos y para determinar ambos cambios y prevalencia de NR para

reducir los niveles de IR, donde nuestras mayores conclusiones fueron; que las mejoras en la performance de fuerza del tren inferior y la reducción del perímetro de cintura pueden explicar mayormente las mejoras en el control glicémico de niños escolares respondedores después de 6 semanas de RT o HIT. En el estudio 5 (capítulo 6) el objetivo fue investigar a) cuales entre 20-variables cardiometabólicas y de performance son R o NR para modificarse benéficamente después de HIT, RT, o CT en mujeres adultas con IR y b) reportar ambos cambios inducidos por el entrenamiento, así como la prevalencia de NR, donde los principales hallazgos fueron; que independiente del modo de ejercicio incluyendo el volumen y la frecuencia de este, el RT tiene una importante habilidad para reducir la prevalencia de no-respuestas para mejorar 20 variables de salud y performance en mujeres con IR. Finalmente, en el estudio 6 (capítulo 7), los objetivos fueron investigar los efectos de un programa de 20 semanas de ejercicio combinado (CT) sobre factores de riesgo cardiovascular así como la composición corporal, la presión arterial y el perfil lipídico entre mujeres adultas con hiperglicemia y reportar la prevalencia de NR para diferentes variables, concluyéndose que; adicionalmente a los beneficios sobre la homeostasis de la glucosa, un programa de CT para mujeres con prediabetes puede disminuir la masa grasa y mejorar el perfil lipídico en términos ‘promedio’, así como mejorar el estatus clínico cambiando desde un ‘alto’ a un bajo/normal riesgo cardiovascular post ejercicio.

En suma, a) HIT y RT muestran similares efectos y prevalencia de NR para mejorar variables de control glicémico en mujeres con IR, b) independiente de la magnitud del grado de control glicémico, existen una similar prevalencia de NR para mejorar en HOMA-IR, c) no existieron diferencias en la prevalencia de NR para mejorar variables metabólicas entre niños escolares con IR de diferente inicio de maduración biológica, pero si para otras variables relacionadas a la salud y la performance, d) las mejoras en la performance de fuerza y las reducciones en el perímetro de cintura pueden explicar los efectos sobre el control glicémico en niños escolares con IR, e) el ejercicio RT tiene una importante habilidad para reducir la prevalencia de no-respuestas para mejorar 20 variables de salud y performance en mujeres con insulino resistencia, y finalmente f) un programa de ejercicio de CT para mujeres con prediabetes reporta tanto R como NR para cambiar es estatus clínico inicial desde un alto a un bajo a un menor riesgo cardiovascular.

Estudio 1 (Capítulo 2)

Introducción/objetivos: Nuestro objetivo fue investigar los efectos y la prevalencia de no-respondedores al ejercicio HIT y al ejercicio de RT en mujeres adultas con IR en parámetros de control glucémico. **Métodos:** Mujeres adultas con IR (edad = 33.5 ± 6.5 años; IMC = 29.9 ± 3.7 kg/m²) fueron asignadas en orden randomizado a un programa

HIT (HIT; $N = 20$) o de fuerza (RT; $N = 20$). Los parámetros glicemia en ayuna, insulina en ayuna y HOMA-IR de control glucémico, así como adicionalmente co-variables de composición corporal, cardiovasculares, y de performance fueron medidas antes y después de 12-semanas en ambos grupos. **Resultados:** Mejoras significativas ($P < 0.05$) en la glicemia en ayuna (-6.6% y -5.8%), insulina en ayuna (-47.2% y -38.1%), y HOMA-IR (-50.0% y -36.3%) fueron identificadas para el grupo HIT y RT, respectivamente después de intervención. No existieron diferencias en la prevalencia de NR entre HIT y el RT para reducir la glicemia (16.6 vs. 29.4%, OR = 1.9; 95% CI 0.4, 10.5), insulina en ayunas (11.1 vs. 11.7%, OR = 1.0; 95% CI 0.1, 8.5), y HOMA-IR 11.1 vs. 11.7%, OR = 1.7; 95% CI 0.2, 11.7) respectivamente para cada grupo, después de intervención; sin embargo, existieron diferencias significativas en la prevalencia de NR en otras co-variables (masa corporal, IMC, pliegue tricípital, masa grasa y masa muscular), cardiovasculares (frecuencia cardiaca en reposo, presión diastólica), y de performance ($1RM_{BC}$, $1RM_{LE}$, $1RM_{SP}$, $1RM_{UR}$) después de intervención. **Conclusiones:** 12-semanas de HIT y RT tienen similares efectos y prevalencia de NR para mejorar variables de control glucémico; sin embargo, existe un diferente prevalencia de NR en otras variables de composición corporal, cardiovasculares, y de performance de fuerza y de endurance en mujeres adultas con IR. Estos hallazgos fueron encontrados con una similar inversión de tiempo/semana de 114 vs. 108 min, respectivamente para HIT y RT.

Estudio 2 (Capítulo 3)

Introducción/objetivos: El ejercicio físico mejora parámetros en promedio, pero existe una amplia variabilidad inter-individual, donde algunos sujetos pueden ser clasificados como respondedores (R) o no-respondedores (NR), especialmente entre poblaciones con altos o bajos niveles de IR. Este estudio midió los efectos del ejercicio HIT y la prevalencia de NR en mujeres adultas con altos y bajos niveles de IR.

Métodos: Cuarenta mujeres adultas fueron asignadas a un programa HIT y analizadas en dos grupos; un grupo con altos niveles de IR (H-IR, 40 ± 6 años; IMC: 29.5 ± 3.7 kg/m²; $N = 20$) y un grupo con bajos niveles de IR (L-IR, 35 ± 9 años; 27.8 ± 2.8 kg/m²; $N = 20$). Variables de composición corporal, cardiovasculares, metabólicas, y de performance variables fueron medidas ante y después de 10 semanas de intervención.

Resultados: Existieron cambios significativos [delta porcentual (1%)] en la glucosa en ayunas, insulina en ayunas, y el modelo homeostático de insulino resistencia de la glucosa (HOMA-IR) en el grupo H-IR (-8.8, -26.5, -32.1%, $P < 0.0001$), donde no se observaron cambios significativos en el grupo L-IR. Ambos grupos mostraron cambios significativos antes y después en otras variables de composición corporal [perímetro de cintura (-5.2, $P < 0.010$, y -3.8%, $P = 0.046$) pliegues tricípital (-13.3, $P < 0.010$, y -13.6%, $P < 0.0001$), supra-iliaco (-19.4, $P < 0.0001$, y -13.6%, $P < 0.0001$), y

abdominal (-18.2 , $P < 0.0001$, and -15.6% , $P < 0.010$]. La presión sistólica disminuyó significativamente solo en el grupo L-IR (-3.2% , $P < 0.010$). Ambos grupos mostraron incrementos significativos en $1RM_{LE}$ ($+12.9$, $P < 0.010$, y $+14.7\%$, $P = 0.045$). Existieron diferencias significativas en la prevalencia de NR entre en grupo H-IR y L-IR para la glicemia en ayunas (25 vs. 95%, $P < 0.0001$) e insulina en ayunas ($P = 0.025$) pero no para HOMA-IR (25 vs. 45%, $P = 0.185$). **Conclusiones:** Independientemente de la magnitud de una enfermedad cardiometabólica (i.e., altos vs. bajos niveles de IR), no existen diferencias en la prevalencia de NR con respecto a mejoras en el HOMA-IR o para co-variables de composición corporal, cardiovasculares y de performance de fuerza después de 10 semanas de HIT en mujeres adultas sedentarias con IR.

Estudio 3 (Capítulo 4)

Introducción/objetivos: Estudios previos tienen observado una significativa heterogeneidad en la magnitud de los cambios metabólicos producidos por el ejercicio físico. Existe una falta de estudios explorando la prevalencia de NR en niños incluyendo otros potenciales factores ambientales como la maduración biológica. El objetivo de este estudio fue comparar los efectos y la prevalencia de NR para reducir los niveles de IR (mediante HOMA-IR) y otras co-variables de composición corporal, cardiovasculares y de performance entre niños escolares tempranamente maduros (EM) y normalmente maduros (NM) después de 6 semanas de ejercicio HIT. **Métodos:** Niños físicamente inactivos (edad 11.4 ± 1.7 años) fueron asignados en orden randomizado a un grupo ejercicio HIT de temprana maduración HIT-EM ($N = 12$) o a un grupo HIT de normal maduración biológica HIT-NM ($N = 17$). La glicemia en ayuna (FGL), insulina en ayuna (FINS) y el HOMA-IR fueron medidos como principales variables, así como la composición corporal [masa corporal, índice de masa corporal (BMI), perímetro de cintura (WC), y los pliegues tricípital (TSF), supra-iliaco (SSF) abdominal (AbdSF)], cardiovasculares presión sistólica (SBP) y diastólica (DBP), y la performance de fuerza [una repetición máxima de extensión de pierna ($1RM_{LE}$) y remo ($1RM_{UR}$) test] fueron medidas antes y después de intervención. Los sujetos respondedores (R) y NR al ejercicio fueron definidos de acuerdo a cambios en el error técnico en las principales variables y co-variables. **Resultados:** No existieron diferencias significativas entre grupos en la prevalencia de NR basados en la glicemia en ayuna, insulina en ayuna y HOAM-IR. No existieron diferencias significativas en la prevalencia de NR para reducir las co-variables masa corporal (HIT-EM 66.6% vs. HIT-NM 35.2%) y presión sistólica (HIT-EM 41.6% vs. HIT-NM 70.5%). Un riesgo [basado en odds ratios (OR)] de casos de NR fue detectado para FGL, OR = 3.2 (0.2, 5.6), y HOMA-IR, OR = 3.2 (0.2, 6.0). Adicionalmente, ambos grupos HIT-EM y HIT-NM mostraron reducciones significativas ($P < 0.05$) en TSF, SSF, pliegue AbdSF, con similares reducciones en la insulina en ayunas y HOMA-IR. El grupo HIT-EM mostró

una reducción significativa en la SBP. El grupo HIT-NM mostró incrementos significativos en $1RM_{LE}$ and $1RM_{UR}$. Un largo tamaño del efecto estadístico fue observado en los cambios pre-post en el TSF de ambos grupos, así como en el SSF del grupo HIT-NM. **Conclusiones:** Aunque no existieron diferencias en la prevalencia de NR para variables metabólicas ente grupos de niños escolares con insulino resistencia y diferente inicio de maduración sexual, existieron otras diferencias en la prevalencia de NR a nivel de las variables masa corporal y presión sistólica, sugiriéndose que la composición corporal, y los parámetros cardiovasculares podrían estar jugando un rol en la prevalencia de NR después de HIT. Estos hallazgos fueron encontrados con varias mejoras a nivel metabólico, composición corporal, presión arterial y la performance de manera independiente de un temprano/normal maduración sexual o independiente de la prevalencia de NR.

Estudio 4 (Capítulo 5)

Introducción/objetivos: Existe escasa evidencia acerca de cómo variables de composición corporal, fuerza muscular podrían mediar las mejoras en el control glucémico tomando en cuenta la variabilidad inter-individual metabólica usando diferentes modos de ejercicio físico. Nosotros examinamos variables ‘mediadoras’ de los efectos de 6 semanas de ejercicio RT y ejercicio HIT en parámetros de control glucémico de niños escolares con IR. Secundariamente, nosotros también determinamos los cambios al ejercicio en términos de aquellos R y NR para disminuir los niveles de IR. **Métodos:** Cincuenta y seis niños físicamente inactivos diagnosticados con IR participaron de un programa supervisado de RT o de HIT durante 6 semanas. Los participantes fueron clasificados de acuerdo a sus niveles de cambios delta post ejercicio usando el $\Delta HOMA-IR$ de acuerdo a aquellos quienes disminuyeron este marcador siendo R ($HOMA-IR < 3.0$ post intervención) y NR (no cambios o valores de $HOMA-IR \geq 3.0$ post intervención). La principal variable fue el HOMA-IR en su asociación con los mediadores de la respuesta glicémica; segundo, los cambios inducidos por ejercicio en el control glucémico y tercero, se incluyó el reporte de R y NR para mejorar la composición corporal, cardiovascular, metabólica y parámetros de performance. **Resultados:** El análisis de mediación reveló que mejoras (reducciones) en la grasa abdominal mediante el perímetro de cintura podrían explicar mejor los efectos (reducciones) de HOMA-IR en niños escolares con insulino resistencia sometidos a ejercicio de RT o HIT. El mismo análisis mostró que el incremento en la fuerza de extensión de piernas se correlacionó con cambios en el HOMA-IR ($\beta = -0.058$; $P = 0.049$). Por lo tanto, un cambio en el perímetro de cintura media la relación de dosis-respuesta entre los cambios de la fuerza (incrementos $1RM_{LE}$) y la reducción de HOMA-IR ($\beta' = -0.004$; $P = 0.178$). El grupo RT y HIT mejoraron variables de composición corporal, fuerza muscular, presión arterial, y

parámetros cardiometabólicos indistintamente de la respuesta glicémica. Ambos grupos de RT respondedores y HIT respondedores respectivamente, tuvieron mejoras en promedio para HOMA-IR, fuerza muscular y marcadores de adiposidad.

Conclusiones: Las mejoras en la fuerza del tren inferior y reducciones en el perímetro de cintura pueden explicar mejormente los efectos del ejercicio en las mejoras del control glucémico en niños escolares con IR después de 6-semanas de participar en ejercicio RT o HIT, mostrando ambos modos de ejercicio similares efectos en la composición corporal y fuerza muscular, independientemente de la variabilidad en la respuesta interindividual metabólica.

Estudio 5 [Aceptado] (Capítulo 6)

Introducción/objetivos: Nosotros investigamos cuáles incluyendo 20 variables de salud y performance, responden o no-responden benéficamente después de HIT, RT o CT en mujeres con IR. Un segundo objetivo fue reportar ambos cambios inducidos por el ejercicio y la prevalencia de NR. **Métodos:** Cuarenta y cinco mujeres con IR fueron asignadas en orden randomizado a uno de los siguientes grupos: HIT (39.2 ± 9.5 años; índice de masa corporal [IMC], 29.3 ± 3.3 , $N = 14$), RT (33.9 ± 9.3 años; BMI, 29.4 ± 5.5 ; $N = 8$), CT (43.3 ± 8.1 años; IMC, 29.1 ± 2.9 ; $N = 10$), y a un grupo control (CG, 40.1 ± 11.4 años; BMI, 28.3 ± 3.5 ; $N = 13$). Nueve variables de composición corporal, 3 de tipo cardiovascular, 3 metabólicas y 5 de performance fueron medidas antes y después de 12 semanas de intervención. **Resultados:** Considerando todas las 20 variables incluidas, el ejercicio RT presentó la menor cantidad de variables no-respondedoras, seguido de los grupos CT y HIT. **Conclusiones:** Independiente del modo de ejercicio, volumen y frecuencia, el RT tiene una importante habilidad para reducir la prevalencia de no-respuestas en la mejora de 20 variables relacionadas con la salud y la performance de mujeres adultas con IR.

Estudio 6 [Enviado] (Capítulo 7)

Introducción/objetivos: La evidencia en favor del potencial beneficio del ejercicio CT para mejorar la comorbilidad asociada a la prediabetes es escasa. Nosotros examinamos los efectos de 20 semanas de ejercicio CT (endurance [ET] + RT) sobre factores de riesgo cardiovascular como la composición corporal, presión arterial, y perfil de lípidos entre mujeres con hiperglicemia. Un segundo objetivo fue reportar la prevalencia de sujetos NR para las diferentes variables. **Métodos:** Mujeres adultas físicamente inactivas con sobrepeso/obesidad e hiperglicemia (edad = 42 ± 6 años; IMC = 30.9 ± 4.8 kg/m²) fueron asignadas en orden randomizado a 20 semanas de un grupo ejercicio CT o a un grupo control (CG), ($N = 14$ /grupo). Índices de comorbilidades para la composición corporal [masa corporal, perímetro de cintura

(WC), masa grasa y libre de grasa], presión arterial y perfil metabólico (colesterol total, C-LDL y colesterol C-HDL, triglicéridos y glicemia en ayuna) fueron medidos antes y después de 20 semanas de intervención. **Resultados:** Al margen de una reducción en la glicemia (-4 mg/dL en promedio, $P = 0.05$), beneficios significativos del CT fueron encontrados para los valores en media en la adiposidad (masa corporal -1.3 kg, $P = 0.026$ y WC -4.0 cm, $P < 0.0001$) y perfil lipídico (colesterol total -12 mg/dL, $P = 0.038$; colesterol-LDL -11 mg/dL, $P = 0.022$; colesterol-HDL +4 mg/dL, $P = 0.003$; y triglicéridos -25 mg/dL, $P < 0.0001$), donde estas variables no mostraron cambios en el grupo control. La masa grasa, masa libre de grasa, presión sistólica y diastólica no presentaron cambios en ambos grupos CT y CG. A nivel individual, la prevalencia de R y NR, fueron: para WC (CT 14% y 86%; CG 0% and 100%), para presión sistólica (CT 36% y 14.2%; CG 14% y 7%), para presión diastólica (CT 0% y 0%; CG 7% y 14%), para el colesterol total (CT 14% y 29%; CG 7% y 28%), C-LDL (CT 21% y 36%; CG 0% y 43%), C-HDL (CT 14% y 50%; CG 14% y 57%) y triglicéridos (CT 21% y 14%; CG 0% y 43%), respectivamente. **Conclusiones:** En suma a los beneficios en la homeostasis de la glucosa, un programa de ejercicio de CT para mujeres con prediabetes puede reducir la obesidad abdominal y mejorar el perfil lipídico en términos 'promedio', así como mejorar el estatus clínico de algunos individuos (i.e., aquellos R) desde un 'alto' hacia un 'normal/bajo' riesgo cardiovascular después de ejercicio.

Chapter 1

**A brief historical remark of responders and non-
responders to exercise-training:
An introduction**

Physical inactivity and inter-individual variability to exercise training

Physical inactivity produce a detrimental effect on both health and performance (Booth, Chakravarthy, Gordon, & Spangenburg, 2002), where exercise training have an important role restabilising the abnormal altered parameters as the case of those physical inactivity related diseases (Colberg et al., 2016). Since almost 30 years ago, Dr Claude Bouchard and colleagues have reported that despite all the beneficial effects benefits in 'mean' terms, there is a wide inter-individual variability to exercise training at level of performance parameters (C. Bouchard et al., 1999; Prud'homme, Bouchard, Leblanc, Landry, & Fontaine, 1984). After that, and considering relevant advances in the exercise sciences, medicine, physiology, genetic, epigenetics, and the use of new technologies of research, several other parameters such as body composition (Churchward-Venne et al., 2015), cardiovascular (Astorino & Schubert, 2014), and metabolic (i.e., cardiometabolic) (Boulé et al., 2005) where exercise training affects positive both health and performance, have been also studied in this inter-individual variability to exercise training (IVRET) approach.

Responders / non-responders terms and criteria classification

The main part of the IVRET studies express this variance in the effects of the exercise training from one to another subject as responders and non-responders. This mean that following the same exercise-stimulus, some subjects may achieve positive benefits (i.e., responders – R), whereas other subjects may experience a worsened or unchanged response after training (i.e., non-responders – NR). Thus, despite literature have described several others terms such as compensators/non-compensators, adverse response (Claude Bouchard et al., 2012), low/high responders (Davidsen et al., 2011), and responders/non-responders (Astorino & Schubert, 2014), both last R and NR terms are more commonly used from the original authors (Sisson et al., 2009) to categorize the beneficial and no beneficial/no change from exercise training to some predicted outcome to improve.

On the other hand, when the first criteria classification used was those values positive or negative from '0' in order to detect R and NR for example at performance outcomes (Sisson et al., 2009), but actually, other more standardized criteria classification is the technical error of measurement (TE), due to this consider the error of two or more measurements of the devices used for registered the behaviour of some performance or health-related outcome (Claude Bouchard et al., 2012). However, despite the IVRET is a phenomenon widely recognize in exercise training studies, the more appropriate criteria for R and NR classification can differ or is matter of debate in order to the nature of the study, including other criteria such as a) clinical criteria for R

and NR (i.e., some clinical cut-off points for example in the case of fasting glucose when hyperglycaemic individuals decrease more than 100 mg/dL, they can be classified as R or NR), or b) when some athletes are able to get some new threshold, and this is into some relevant sport aim, they could also be classified as R or NR.

Inter-individual variability to exercise training for improving performance

Environmental and genetic factors have been described as the main responsible for this phenomenon (Mann, Lamberts, & Lambert, 2014); however, not at all environmental factors (i.e., different mode of exercise or health status for example) have been explored. More yet, although part of these and others factors have been reported to influence more/less R and NR, there is a lack of studies showing how more NR prevalence are there after a different mode of training (i.e., endurance [ET], resistant [RT], high-intensity interval [HIT], or concurrent training [CT]), or the previous health status before exercise (i.e., the degree of disease of a sample/subject), or for example the influence of the biological maturation in children in the exercise R and NR prevalence. In this sense, few information also exist about what are the main outcomes ‘mediators’ of the exercise response where after exercise have been identified both R and NR. When initially the main focus exploring R and NR was based on performance outcomes such as the maximum oxygen consumption [VO₂max] (C. Bouchard et al., 1999) (Figure 1).

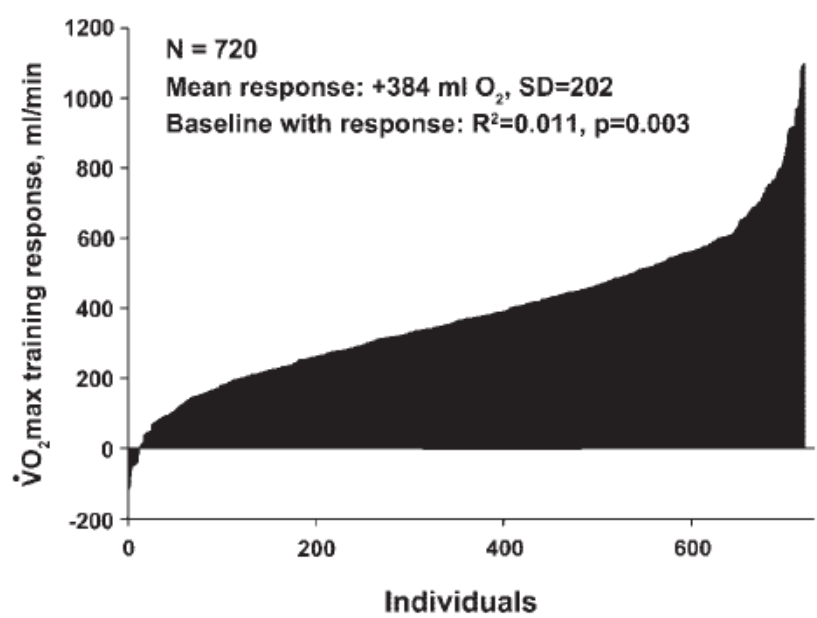


Figure 1. Inter-individual variability in the maximum oxygen uptake from the HERITAGE study. Original from the study of (Bouchard and Rankinen, 2001).

This IVRET in the VO₂max, was tested genetically in the participants of the HERITAGE study, where was describes a high familial aggregation in the response to show a low or high VO₂max (Figure 2).

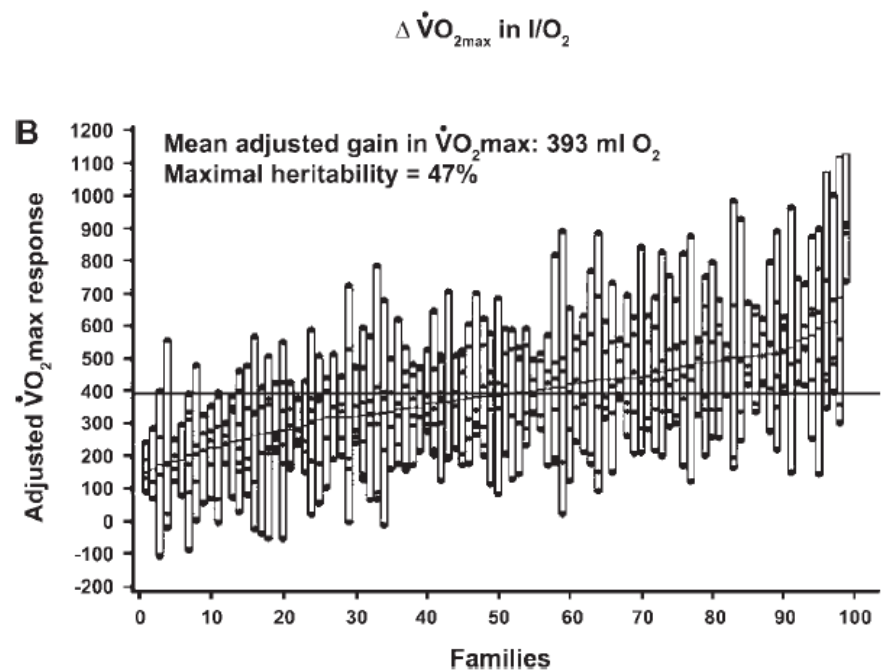


Figure 2. Inter-individual variability in x families from the Canadian study HERITAGE. Original from the study of (Bouchard et al., 1999).

Physical inactivity and low-glucose control

With the modernity, the sedentary and physically inactive lifestyle of the adult and children population, where obesity-related diseases such as IR, type 2 diabetes mellitus (T2DM) and hypertension (HTN) have been increased in several countries around the world including Latinoamerican countries (Celis-Morales et al., 2015), there are strong evidence of the exercise training as a therapy to these cardiometabolic (i.e.: that include overweight/obesity, high blood pressure, and/or additionally a low glucose control) diseases, for example to one of the most common metabolic disease such as the IR that are suffering both adults (Abdul-Ghani & DeFronzo, 2010) and children (R. Burrows et al., 2015).

The IR is the intermediate state between a healthy and a T2DM disease, which is characterized by an inability of the insulin to translate the glucose from the plasma to into muscles (Abdul-Ghani & DeFronzo, 2010). The Pancreas doing a high but erroneous effort for decreasing and compensate the plasma glucose level need to increase a compensatory hyperinsulinemia, but with a final state of the β -cell decreasing progressively their insulin production (Abdul-Ghani & DeFronzo, 2010). In a normal state, being adults physically active, skeletal muscle is the site of disposal of more than 80% of ingested glucose by insulin-stimulated way and the liver responsible until one third (DeFronzo, Gunnarsson, Bjarkman, Olsson, & Wahren, 1985). Thus, IR is a common metabolic disease of physically inactive population including adults and children.

Inter-individual variability to exercise training as R and NR following cardiometabolic risk factors

The HERITAGE study that consisted in 6-months of endurance exercise for participants of different age, sex, and ethnic groups reported that x subject do not improved HDL-C, and others x participants do not modified the blood pressure at a specific 50-watt of workload (C. Bouchard & Rankinen, 2001a). Thus, as an early finding from Bouchard and colleagues, at level of heart rate and blood pressure during exercise, there was reported a different response in both outcomes (Figure 3 and Figure 4) shows the IVRET in the HDL-C and systolic BP during exercise.

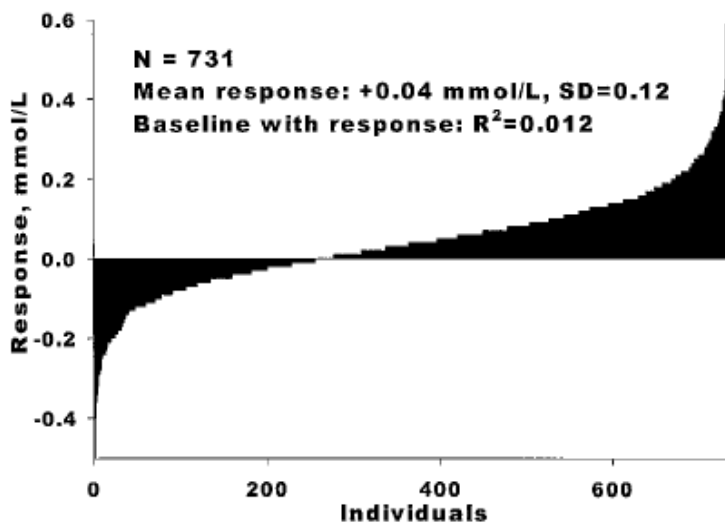


Figure 3. IVRET in HDL-C from the HERITAGE study. Original from the study of (Bouchard et al., 1999).

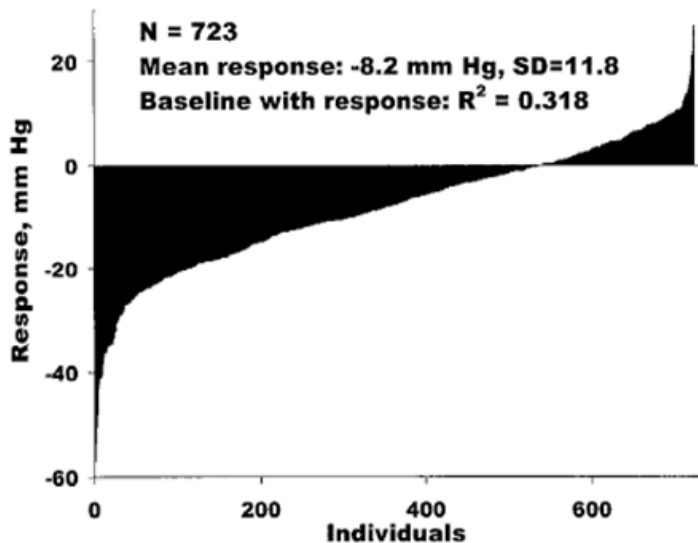


Figure 4. IVRET in systolic blood pressure at 50 watt of exercise, data from the HERITAGE study. Original from the study of (Bouchard et al., 1999).

More recently (Astorino & Schubert, 2014) showed that not at all of participants from HIT improve fat oxidation after 2-weeks (Figure 5). In this study, the authors also reported that being NR to one outcome do not implies to be R to another outcome.

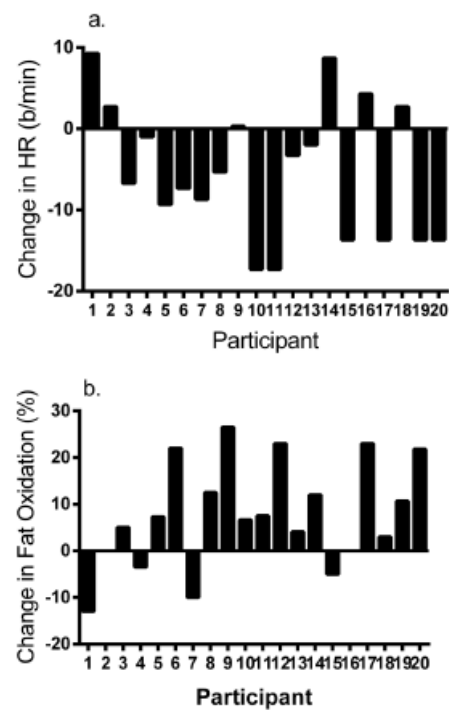


Figure 5. Individual responses for a change in the exercise heart rate (a) and in lipid oxidation in response to 2-weeks of HIT. Original from the study of (Astorino & Schubert, 2014).

In others studies, (Claude Bouchard et al., 2012) reported from a sample of the same HERITAGE study, that from 1687 subjects including man and women, where, 126 participants (8.4%) had an adverse change to fasting insulin after 6-months of exercise and the numbers of adverse responders were 12.2% for systolic blood pressure, a 10.4% for triglycerides, and a 13.3% for high-density lipids (HDL-C). Additionally, around a 7% of the subjects showed an adverse response in two or more risk factors studied (Figure 6).

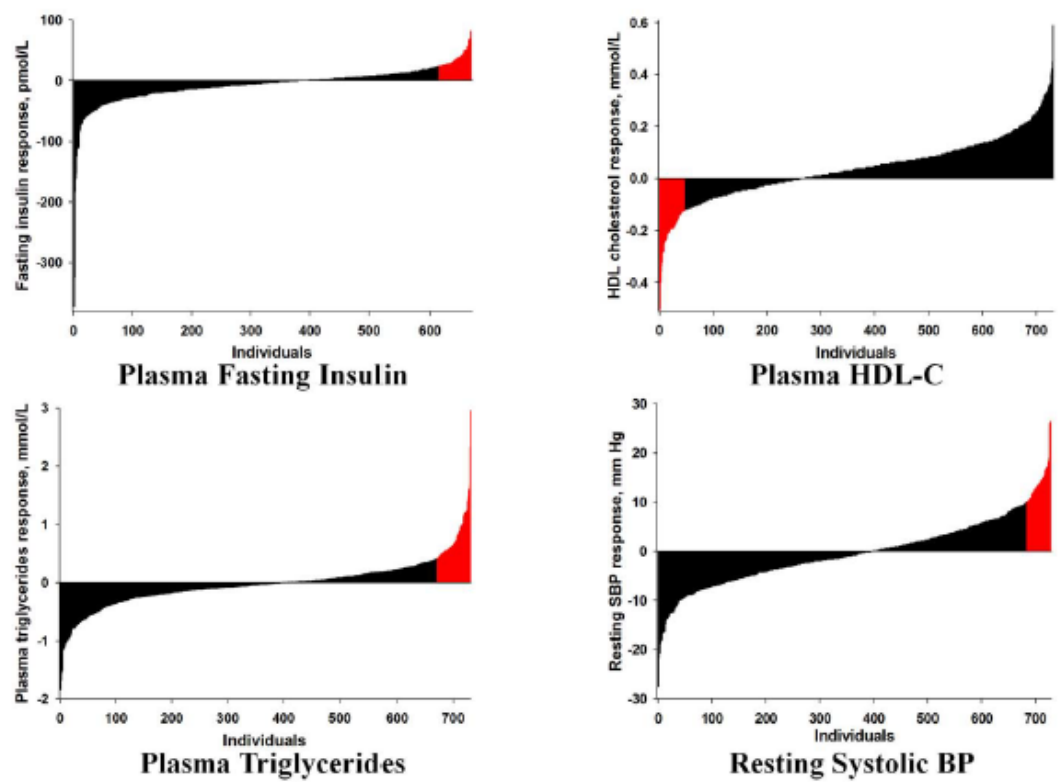


Figure 6. Distribution of the response to the HERITAGE exercise program with adverse responders highlighted in red for decreasing fasting insulin, HDL-C, triglycerides and systolic blood pressure. Original from the study of (Bouchard et al, 2012).

Prevalence of non-responders among populations with cardiometabolic risk factors

Summarizing the evidence, there is a wide IVRET, where while some subjects achieve benefits being R, other could no change or to show a worsened response named NR. But, predicting that after any exercise training program It could be possible to find out an undetermined amount of percentage of NR cases (i.e., prevalence of NR), It is yet unknown how more prevalence of NR are there after environmental or endogenous factors such as the mode of training, the health status, or the biological maturation in children. Thus considering that IR is the previous state for T2DM, where exercise training have a demonstrated role as a therapy (C. Álvarez et al., 2014; Hawley & Lessard, 2008; Marson, Delevatti, Prado, Netto, & Kruel, 2016a), to know how much percentage of NR prevalence can be there after these factors could contribute to several strategies in order to avoid T2DM for example, a) detecting exercise modalities with less NR prevalence could benefit more population of this profile, b) establishing specific cut-off points for insert exercise programs at public health to those health status before T2DM state, c) detecting critical biological maturation development to intervene with exercise strategies in children with IR, and d) identifying the main mediators outcomes between the exercise stimuli and the IR decreases markers.

Aims, layouts and hypothesis of the thesis

Study 1

Effects and prevalence of non-responders after 12-weeks of high-intensity interval or resistance training in women with insulin resistance: a randomized trial.

Aim: To investigate the effects and prevalence of NR to HIT and RT in adult woman with IR on glucose control parameters. (Chapter 2).

Study 2

Prevalence of non-responders for glucose control markers after 10-weeks of high-intensity interval training in adult women with higher and lower IR.

Aim: This study assessed the effects of HIT and the prevalence of NR in adult women with higher and lower levels of insulin resistance. (Chapter 3).

Study 3

Effects of 6-weeks high-intensity interval training in schoolchildren with insulin resistance: influence of biological maturation on metabolic, body composition, cardiovascular and performance non-responses.

Aim: To compare the effects and prevalence of NR to improve the IR level (by HOMA-IR), as well as to other body composition, cardiovascular, and performance co-variables, between early (EM) and normal maturation (NM) in IR schoolchildren after 6-weeks of HIT. (Chapter 4).

Study 4

Metabolic effects of resistance or high-intensity interval training among glycaemic control-nonresponsive children with insulin resistance.

Aim: We examined 'mediators' to the effects of 6-weeks of RT or HIT on glucose control parameters in physically inactive schoolchildren with IR. Second, we also determined both training-induce changes and the prevalence of R and NR to decrease the IR level. (Chapter 5).

Study 5

Inter-individual responses to different exercise stimuli among insulin-resistant women.

Aim: to investigate which among 20-cardiometabolic and performance outcomes do and do not respond to HIT, RT, or CT in IR adult women. A secondary aim was to report the training-induced changes and the prevalence of NR. (Chapter 6).

Study 6

Concurrent training and prediabetes comorbidities: an analysis of non-responders using clinical cutoff points.

Aim: To investigate the effects of a 20-week CT intervention on cardiovascular risk factors such as body composition, blood pressure and lipid profile among adult women with hyperglycaemia. A secondary aim was to report prevalence of NR for the different study outcomes. (Chapter 7).

Hypothesis

Hypothesis 1: The prevalence of NR is independent of the mode of training in adult women with IR. (Study 1, chapter 2).

Hypothesis 2: The prevalence of NR is independent of the glucose control degree in adult women with IR. (Study 2, chapter 3).

Hypothesis 3: The prevalence of NR is independent of the biological maturation starting in schoolchildren with IR. (Study 3, chapter 4).

Hypothesis 4: The main ‘mediators’ of the potential glucose control improvements in schoolchildren are the performance outcomes. (Study 4, chapter 5).

Hypothesis 5: The most power exercise mode for improving 20-cardiometabolic and performance outcomes is RT. (Study 5, chapter 6).

Hypothesis 6: The prevalence of NR to change their clinical status after the CT exercise is independent of the beneficial effects in mean terms. (Study 6, chapter 7).

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Chapter 2

Effects and prevalence of non-responders after 12-weeks of high-intensity interval or resistant training in adult women with insulin resistance: a randomized trial

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Effects and prevalence of non-responders after 12-weeks of high-intensity interval or resistant training in adult women with insulin resistance: a randomized trial

Abstract

Background/aims: Our aim was to investigate the effects and the prevalence of NR to HIT and RT in adult women with IR on glucose control parameters. **Methods:** Sedentary overweight/obese IR adult women (age = 33.5 ± 6.5 years; BMI = 29.9 ± 3.7 kg/m²) were randomly assigned to a tri-weekly HIT program (HIT; $N = 20$) or resistant training (RT; $N = 20$). Glucose control fasting glucose, fasting insulin and HOMA-IR, as well as additional body composition, cardiovascular, and muscle, and endurance performance co-variables were measured before and after 12-weeks in both intervention groups. **Results:** Improvements ($P < 0.05$) in the fasting glucose (-6.6% and -5.8%), fasting insulin (-47.2% and -38.1%), and HOMA-IR (-50.0% and -36.3%) were identified to HIT and RT group, respectively after training. There were no differences in the NR prevalence between HIT and RT for decreasing fasting glucose (16.6 vs. 29.4%, OR = 1.9; 95%CI 0.4, 10.5), fasting insulin (11.1 vs. 11.7%, OR = 1.0; 95%CI 0.1, 8.5), and HOMA-IR 11.1 vs. 11.7%, OR = 1.7; 95%CI 0.2, 11.7) respectively to each group, after intervention; however, there were significant differences in the NR prevalence in other body composition (body mass, BMI, tricipital skinfold, fat, and muscle mass), cardiovascular (heart rate at rest, diastolic blood pressure), and performance co-variables included ($1RM_{BC}$, $1RM_{LE}$, $1RM_{SP}$, $1RM_{UR}$) after intervention. **Conclusions:** 12-weeks of HIT and RT have similar effects and NR prevalence to improve glucose control variables; however, there is different NR prevalence in other body composition, cardiovascular, strength and endurance performance measurements in IR adult women.

Key words: glucose control; non-responders; risk factors; insulin resistance; high-intensity interval training, resistant training

Introduction

When exercise training is applied with a setting that alters the normal homeostasis, it may produce not only a preventive (Sheri R Colberg et al., 2010) but also a therapeutic role in subjects with altered glucose control, such as type 2 diabetes mellitus (T2DM) (C. Alvarez et al., 2016; Little et al., 2011). T2DM is a highly prevalent disease associated with different public health problems, such as spending, morbidity, and mortality (Shaw, Sicree, & Zimmet, 2010; Zhang et al., 2010). However, prior to T2DM diagnosis, the previous IR stage, when exercise is also a key tool, is inclusive more prevalent (SOCHED, 2014). Thus, a minimum of 150 min/week of moderate to vigorous aerobic exercise, in association with 2-3 sessions per/week of strength training, has been recommended in the current American Diabetes Association and American College of Sport Medicine guidelines (Sheri R Colberg et al., 2010). Unfortunately, despite all benefits in ‘mean’ terms, there is a wide inter-individual variability to exercise training (IVRET) (Astorino & Schubert, 2014; Churchward-Venne et al., 2015; Higgins, Baker, Evans, Adams, & Cobbold, 2015; King, Hopkins, Caudwell, Stubbs, & Blundell, 2008; Moker, Bateman, Kraus, & Pescatello, 2014; Winett et al., 2014). This indicates that following the same stimulus, some subjects may achieve positive benefits (i.e., responders-R), whereas other subjects may experience a worsened or unchanged response after training (i.e., non-responders-NR) (Sisson et al., 2009). Environmental and genetic (Mann et al., 2014) factors have been described as the main reasons for this phenomenon; however, not all potential environmental factors (i.e., different mode of exercise or health status) have been investigated.

The prevalence of NR (i.e., percentage of NR after training intervention) has been reported with respect to several variables, including endurance (ET) (Claude Bouchard et al., 2012; Yates et al., 2013), high-intensity interval (HIT) (Astorino & Schubert, 2014) and resistant training (RT) (Churchward-Venne et al., 2015; Moker et al., 2014), different populations such as obese (King et al., 2008), altered glucose control (Winett et al., 2014), T2DM (Higgins et al., 2015), and healthy subjects (Astorino & Schubert, 2014), and including short (Higgins et al., 2015) or long interventions (Moker et al., 2014); however, different methodological NR classification criteria have been implemented among the studies. In brief, studies have used terms such as low/high responders (Davidsen et al., 2011), non-responders/responders (Manthou, Gill, Wright, & Malkova, 2010), and adverse response (Claude Bouchard et al., 2012), among other terms. For example, after a HIT protocol of 12-weeks, approximately 30% of the subjects were NR with decreasing heart rates, and 20% of the subjects did not increase fat oxidation (Astorino & Schubert, 2014). Six weeks of HIT did not improve the area under the curve of the oral glucose tolerance test (OGTT) with 50% NR, and ~61.5% were NR to improvements in diastolic blood pressure (Higgins et al., 2015).

Twenty-four weeks of RT resulted in 23% NR to a decrease in body mass and 1% NR to an increase in strength performance in leg extension exercises (Churchward-Venne et al., 2015). After 12-weeks of RT, there were a NR prevalence of 60.9% and 59.1% to a decrease in systolic and diastolic blood pressure, respectively (Moker et al., 2014). In pre-diabetic patients, 12-weeks of RT resulted in 44% NR to an improvement in OGTT (Winnett et al., 2014). Following data compilation from five HIT-based studies, 4-weeks of training resulted in 22% NR to an improvement in endurance performance. A different NR prevalence has been reported for several risk factors of T2DM; however, none of these studies has reported the training-induced changes and the prevalence of NR to cardiometabolic risk factors IR subjects in a comparison of different modes of exercise, such as HIT and RT. Thus, it remains unclear which mode of training may generate an increased or decreased amount of NR after interventions; this information will be useful to public physical activity programs that are offered in 'mean terms' to the population to achieve more effectiveness and to massive strategies in this area. Furthermore, it is relevant to understand the unexplored environmental factors that may be related to eliciting an increased or decreased the NR prevalence in order to plan future well-designed genetic studies.

In brief, without body composition changes, 2-weeks of HIT significantly decreased the homeostasis model assessment of insulin resistance (HOMA-IR) of adult T2DM subjects (Shaban, Kenno, & Milne, 2014). In a similar cohort, after 2-weeks of HIT, there was a significant decrease in the average 24-h blood glucose concentration of -13.1% in adult subjects (Little et al., 2011). After 16-weeks of HIT, other authors have reported a decrease in the fasting glucose of -14%, as well as the body mass in -2.2%, and an increase in the endurance performance of +9.8% (by the 2 km walking test) (C. Alvarez et al., 2016). Twenty-weeks of RT plus a weight loss strategy have demonstrated improvements in decreasing fasting glucose of -17.3% compared with -10.6% in weight loss alone (Dunstan et al., 2002). Furthermore, after 11-weeks of RT increased the strength performance in the lower limb muscles of active men in 23% (Izquierdo et al., 2006). Interestingly, 16-weeks of progressive RT has been demonstrated to improve the submaximal and maximal endurance performance capacities (Izquierdo et al., 2003). Thus, short and long HIT and RT programs improve cardiometabolic risk factors related to the prevention and treatment of T2DM, as well as the strength and endurance performance in populations without or with low glucose control.

These preliminary studies are promising and appear to suggest that a short intervention time of commitment exercise may be sufficient to maintain or improve cardiometabolic health and physical fitness if the exercise that is performed is HIT or RT. Cardiometabolic factors may have biological potential to serve as a therapeutic

target for the primary and secondary prevention of T2DM, as well as in clinical settings. However, due to the benefits of improving risk factors associated with T2DM, knowing that IVRET occurs, yet being that some of the environmental factors presumably implicated in this phenomenon are unclear such as the mode of training, these findings may have important practical and clinical implications to practitioners and for the public health perspective. Thus, the aim of the present study was to investigate the effects and prevalence of NR to improve glucose control parameters after 12-weeks of HIT or RT in sedentary adult women with IR.

Material and methods

Participants and study design

We assessed adult overweight or obese (BMI between 25 and 35 kg/m²) women with an established diagnosis (by our research team) of insulin resistant for at least x 1-month and no more than 3-months. The eligibility criteria included fasting hyperglycemia > 100 mg/dL and < 126 mg/dL (S. R. Colberg et al., 2010) and HOMA-IR > 2.6, x no drug therapy during the previous 3 months, physically inactive (according to the International Physical Activity Questionnaire (IPAQ) previously validated in a Chilean population, an IPAQ score of < 600 MET min/wk) (Seron, Munoz, & Lanas, 2010), non-involvement in regular physical activity or an exercise program during the previous 6-months, and with no family history of T2DM. Patients with cardiovascular contraindications to exercise, histories of stroke, asthma or chronic obstructive pulmonary disease, musculo-skeletal disorders, or smokers were not included in the study. A minimum of 70% of exercise program compliance was required for the intervention group patients to be included in the final statistical analyses.

Seventy-three IR women (age 25 to 40 years), who were patients of the Family Healthcare Center Tomas Rojas of Los Lagos (Chile) were invited in the first screening stage by a telephone call with explanations regarding the study aims; the women who agreed to participate in the present investigation were called for a second stage of formal description regarding the study. The patients underwent a structured history, medical record review, and physical examination by a physician for the assessment of eligibility criteria. Using a computer-generated random assignment, 40 IR adult women who were randomly assigned in a 1:1 ratio to 12-weeks of HIT or RT were included in the study (Figure 1). After the follow-up, 35 subjects were included in the final sample analyzed, including high-intensity interval training (HIT, $N = 18$, age = 38.0 ± 8.0 years, BMI = 30.5 ± 3.0 kg/m²) and resistant training (RT; $N = 17$, age = 33.0 ± 7.0 years, BMI = 29.4 ± 4.4 kg/m²) interventions. Plasmatic glucose control parameters, including fasting glucose, fasting insulin, and HOMA-IR, as well as other body composition (body mass, body mass index [BMI], waist circumference, tricipital, supra-iliac, and abdominal skinfold), cardiovascular (heart rate at rest and systolic/diastolic blood pressure), strength (one repetition maximum of biceps curl [1RM_{BC}], leg extension [1RM_{LE}], shoulder press [1RM_{SP}], and upper row [1RM_{UR}]), and endurance performance (by the 2 km walking test [2KMWT]) co-variables were assessed before and after the 12-weeks follow-up in both groups. The patients in the HIT and RT groups performed exercise sessions three times per week. All patients in the intervention groups were oriented to maintain their daily living physical activity and dietary patterns before and after the intervention period. The present study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Family

Healthcare Center Tomás Rojas of Los Lagos (Number 03052015). All volunteers read a detailed description of the study protocol and provided written informed consent.

Responder and non-responder classification

Using previously established criteria in exercise interventions (Bonafiglia et al., 2016), the inter-individual variability to exercise training of the subjects were categorized as responders (R), and non-responders (NR) using the typical error measurement (TE). The TE was calculated for the main outcomes (fasting glucose, fasting insulin and HOMA-IR), as well as to the other co-variables as described previously (Will G. Hopkins, 2000) using the following equation:

$$TE = SD_{diff} / \sqrt{2}$$

Where SD_{diff} is the variance (standard deviation) of the difference scores observed between the 2 repeats of each test. A non-responder (NR) for fasting glucose, fasting insulin, HOMA-IR, as well as to all the others co-variables included was defined as an individual who failed to demonstrate an increase or decrease (in favor of beneficial changes) that was greater than 2 times the TE away from zero. A change beyond 2 times the TE means that there is a high probability (i.e. 12 to 1 Odds) that this response is a true physiological adaptation beyond what might be expected to result from technical and/or biological variability (Will G. Hopkins, 2000).

Blood analyses

Blood samples (4 ml) were collected before and after the 12-weeks of follow-up, in the morning and after a 10-h overnight fast. The post-training blood sampling of the HIT patients was performed at least 48 h after the last exercise session to avoid an acute effect of exercise. The samples were placed in ice and centrifuged at 4,000 rpm for 5 min at -4°C . The plasma samples were immediately transferred to pre-chilled microtubes and stored at -20°C for subsequent analysis. The plasma glucose was analyzed via enzymatic methods using standard kits (Wiener Lab Inc., Rosario, Argentina) on an automatic analyzer (Metrolab2300 Plus™, Metrolab Biomed Inc., Buenos Aires, Argentina). The fasting insulin was analyzed via RIA (DPC, Los Angeles, CA, USA). The insulin resistance levels were calculated by the formula of the homeostasis model assessment: $\text{HOMA-IR} = \text{fasting glucose} * \text{fasting insulin} / 405$ (Matthews et al., 1985).

Body composition and cardiovascular measurements

The measurements were performed during 3 stages before intervention. One week before and after the 12-weeks follow-up, anthropometric and cardiovascular measurements were performed. The body mass (kg) was measured (to the nearest 0.1 kg) using a professional scale (Health o Meter™ Professional, Sunbeam Products Inc., Chicago, IL, USA). The height (m) was assessed using the same machine to the nearest 0.1 m of accuracy. BMI was calculated as the body mass divided by the height squared (kg/m^2).

The waist circumference (cm) was measured to the nearest 0.1 cm, using a flexible and inextensible measuring tape (Hoechstmass™, Sulzbach, Germany). Three site skinfold thickness was performed (tricipital, supra-iliac, and abdominal) using a Languet™ skinfold caliper (Beta Technology Inc., Santa Cruz, California, USA), following the protocols of the International Society for the Advance of Kinanthropometry (Marfell-Jones, 2006). The fat mass (%) and muscle mass were assessed via bioimpedance using a digital scale (Omron HBF-INT™, Omron Healthcare Inc., Lake Forest, IL, USA). This procedure was conducted without metal and watches to increase the precision; the average of three measurements was used. The systolic and diastolic blood pressures were determined using an automatic monitor (Omron HEM 7114™, Omron Healthcare Inc., Lake Forest, IL, USA) in triplicate (2-min interval between measurements) and after 15 min of rest with the subjects in a seated position. The heart rate at rest was measured using a monitor (ProTrainer 5™, Polar Electro Inc., Kempele, Finland) with at least 15 min of rest.

Performance assessment

The strength performance was assessed one week before and after intervention via a one repetition maximum strength test of biceps curl (1RM_{BC}), leg extension (1RM_{LE}), shoulder press (1RM_{SP}), and upper row (1RM_{UR}). The 1RM_{BC} , 1RM_{SP} , and 1RM_{UR} tests were executed using metal bars and free weights similar to other procedures (Izquierdo et al., 2004). The 1RM_{LE} was executed using an exercise machine (OXFORD™, model EE4002, Santiago, Chile). The four tests were conducted in the morning between 9 and 11 h, and the highest load was reported from three attempts per exercise.

The endurance performance was assessed by the 2KMWT (Laukkanen, Kukkonen-Harjula, Oja, Pasanen, & Vuori, 2000) in an indoor sports court (100 m track), after a 10-min warm-up at low-intensity walking and slow movements involving the knee and ankle joints. The subjects were instructed to walk as fast as possible with

a steady pace and were warned not to run. The heart rate was continuously monitored (ProTrainer 5™, Polar Electro Inc., Kempele, Finland) during the test. To warrant an accurate test, the patients were encouraged to walk faster if their heart rate was less than 75% of the maximum age-predicted heart rate. The time spent and average heart rate during walking in the 2KMWT were measured and used for analysis.

Exercise training interventions

Prior to the intervention, during 3 sessions, all subjects were enrolled in a familiarization period of the HIT and RT protocols and the 1RM test. The HIT group performed a progressive HIT program three times per week for 12-weeks. All exercise sessions were performed on cycle ergometers (OXFORD™, model BE2601, OXOFORD Inc., Santiago, Chile). The progressive HIT program consisted of high-intensity intervals of work (cycling) interspersed with inactive (without movement over the bicycle) recovery periods. The patients had their heart rate continuously monitored (ProTrainer 5™, Polar Electro Inc., Kempele, Finland) and were oriented to maintain their cycling between the range of 8 to 10 of subjective effort perception of the modified Borg scale (Emmanuel Gomes Ciolac, Mantuani, & Neiva, 2015). This subjective intensity corresponded to all intervals of work between 70–100% of the reserve heart rate (Karvonen, 1988). The total intervals of work were 12 to HIT.

The participants in the RT group also performed a progressive RT program three times per week for 12-weeks. Four exercises were executed per session; biceps curl, shoulder press, and upper row, which were performed using free weights and metal bars, and leg extension using the previously described exercise machine to 1RM_{LE}. All sessions in both programs were supervised by an exercise specialist. The RT program consisted of an interval of work (performing voluntary extension/contraction) during 60 s in which a range of 8 to 10 of the subjective effort perception of the modified Borg scale was reached in the final 55-60 s. The quantitative intensity in the 1RM ranged from 20 to 40% of the 1RM at the first of the study and was changed post-intervention to between 25 and 50% of the 1RM at the final intervention period. Each interval of work was interspersed by an inactive (seated position) recovery period of 120 s. Each interval of work was repeated 3 times in the four exercises (1:2:3). The total intervals of work were 12 to RT. Each training session was performed in the morning from 9 to 12 h throughout the 12-week period. All subjects had a good exercise tolerance, and none of the participants reported an injury. The exercise compliance was HIT $86.7 \pm 6\%$ and RT $83.3 \pm 7\%$ during the follow-up. A detailed description of the HIT and RT is presented in (Table 1).

Table 1. Characteristics of the two mode of exercise training applied.

Variable	HIT	RT
Exercises N° (mode/type of exercise)	1 (Cycling)	4 (Leg-extension, biceps-curl, shoulder-press, rowing)
Duration of interval of work (s)	60	60
Duration of interval of rest (s)	120	120
Number of intervals of work (N°)	12	12
Number of recovery bouts* (N°)	13	12
Qualitative intensity in Borg scale 1-10 (pts)	8-10	8-10
Quantitative intensity by heart rate maximum (%)	70-100	-
Quantitative intensity 1RM (%)	-	20-40
Cadence (rpm)	50-70	-
Velocity (km/h)	20-40	-
Volume of work / session (min)	12	12
Volume of rest / session (min)	26	24
Total time investment / session (min)	38	36
Total time investment / week (min)	114	108
Total time investment / 12-weeks (h)	22.8	21.6

HIT: high-intensity interval training group; RT: resistant training group; N°: numbers. * All sessions started and ended with a recovery bout respectively for each program.

During each HIT and RT exercise session, the participants adhered to the 45 kcal·kg⁻¹·min⁻¹ energy expenditure/session (12 min to HIT and RT, respectively) format, which was equivalent to ~540 kcal of expended energy/week at the end of the training and cool-down/session (26-24 min to HIT and RT, respectively), with a total exercise time/session (refer to total time investment/session (Table 1) range of 38 to 36 min and a final relaxation/cool-down period/session of 26-24 min for HIT and RT respectively.

Statistical analyses

Data are presented as the mean ± standard deviation (SD). Normality and homoscedasticity assumptions for all data were checked using the Shapiro-Wilk and Levene tests, respectively. The Wilcoxon test was used for the non-parametric data. One-way ANOVA was conducted to identify differences between the baseline groups. ANCOVA analysis was conducted for the diastolic blood pressure as a result of the baseline differences using anthropometric co-variables. A repeated-measures ANOVA of 2 times (groups x time) was used to determine differences in all dependent variables between the pre and post 6-week tests using each group x time. After the intervention, the TE were calculated for the pre-post changes for each dependent variable. The subjects were categorized as R and NR according to the previously described criteria of 2 TE (Bonafiglia et al., 2016). The Bonferroni *post hoc* test was applied to establish differences among groups. To identify differences between the R and NR from the HIT and RT groups, the Chi-Square test (X²) was used for categorical variables. The odds ratio (OR) to suffer a NR was applied in both NR categorical glucose control and other co-variables between the groups in which an OR ≥ 2 fold was considered high risk to suffer a NR. All statistical analyses were performed with SPSS statistical software

version 18 (SPSS™ Inc., Chicago, Illinois, USA). The alpha level was fixed at $P<0.05$ for statistical significance.

Results

Follow-up

Two patients in the HIT group were lost to follow-up because they did not have the minimal exercise training compliance of 70% ($N = 2$), and three subjects were lost to follow-up in the RT group for the same reasons ($N = 3$). Thus, 35 overweight or obese insulin resistant adult women completed the 12-weeks follow-up and were included in the final analysis (Figure 1).

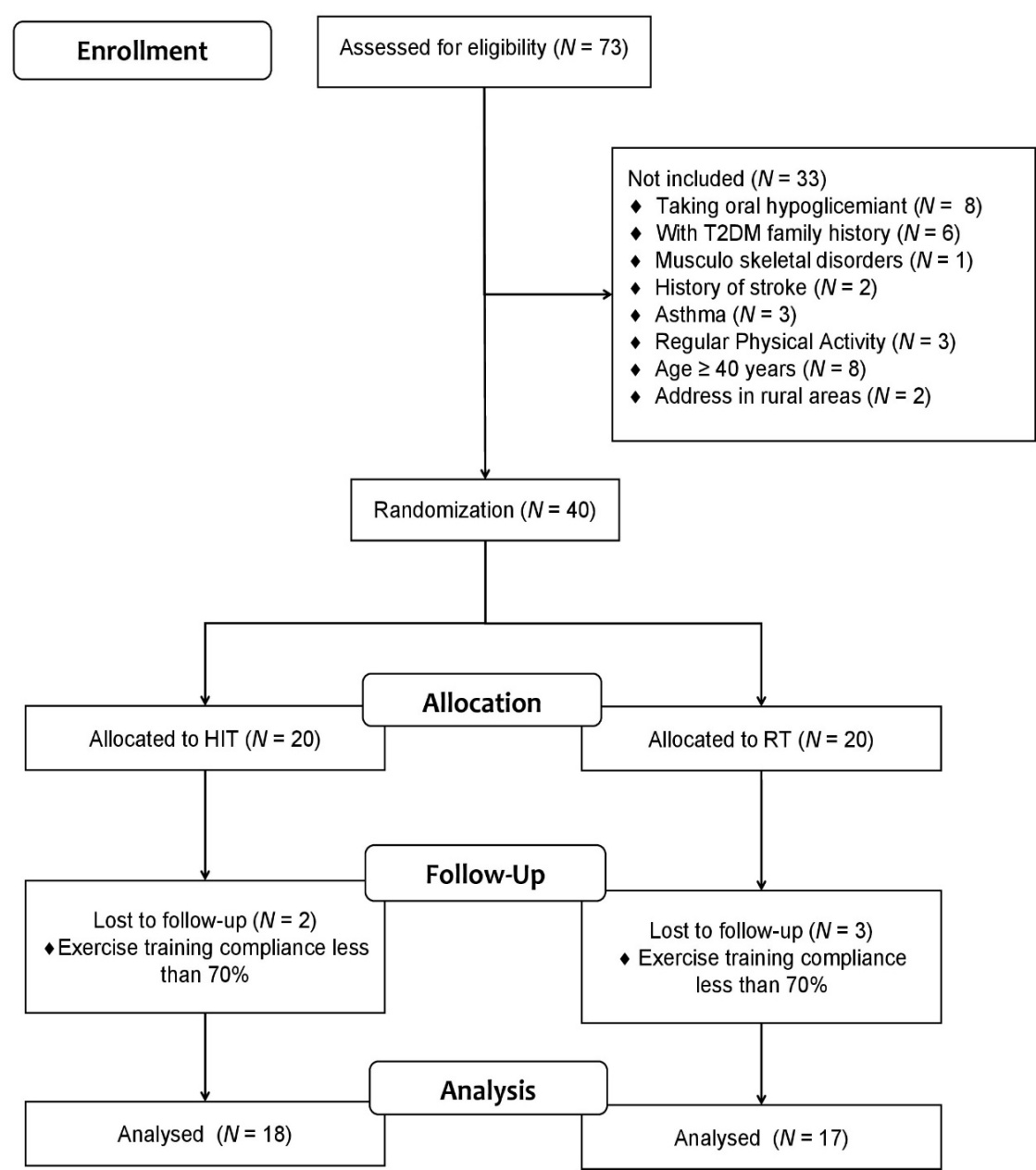


Figure 1. Study design.

Baseline

Significant baseline differences between the HIT and RT groups were identified in the diastolic blood pressure (Figure 2).

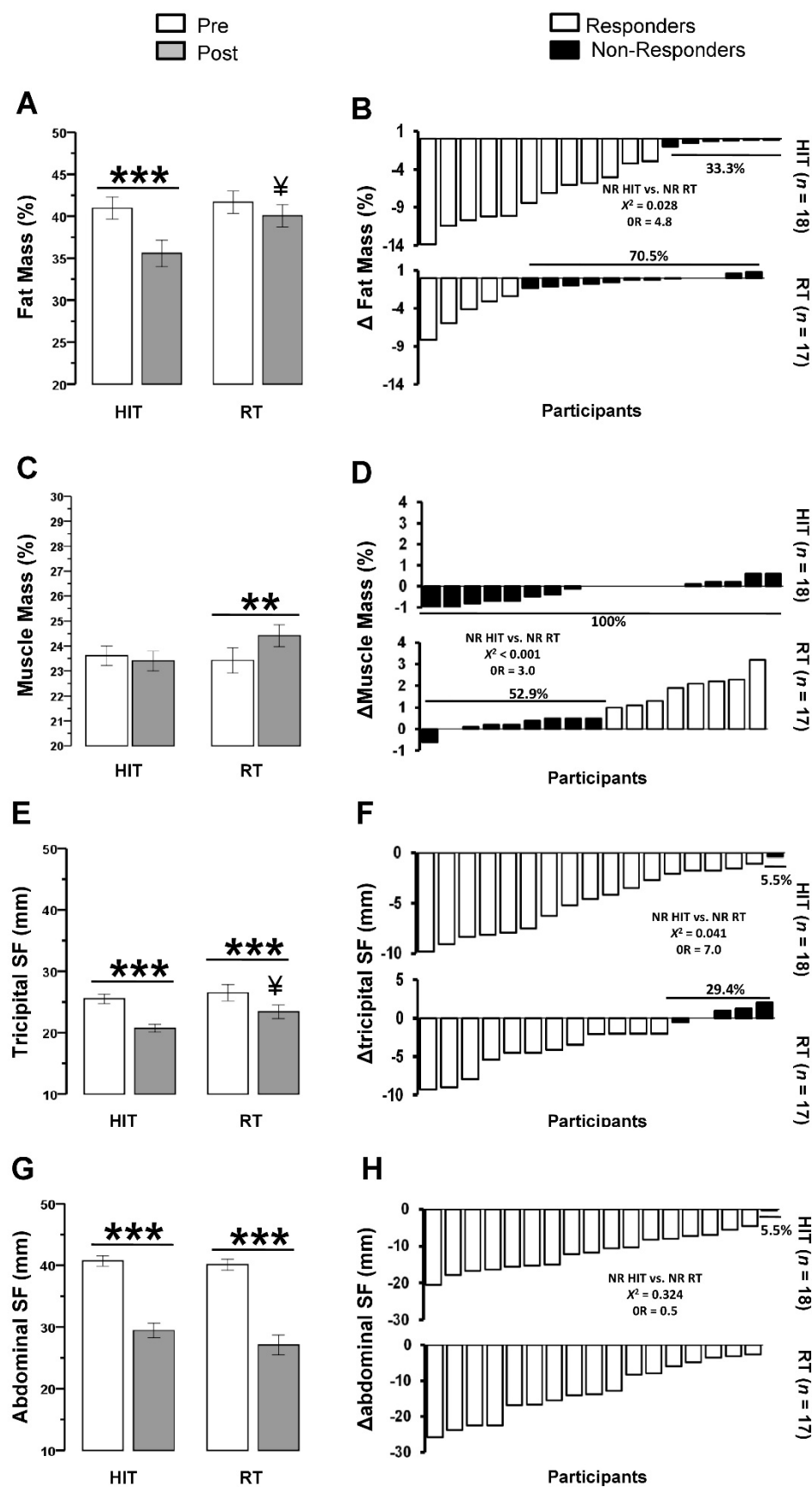


Figure 2. Average changes and non-responder prevalence to decrease fat mass (A, B), to increase muscle mass (C, D), to decrease tricipital (E, F) and abdominal skinfold after 12-weeks of HIT or RT in insulin resistant adult woman. HIT: high-intensity interval training group. RT: resistant training group. **Significant difference from baseline within group at level $P < 0.001$. *** Significant difference from baseline within group at level $P < 0.0001$. ≠ Significant difference vs HIT group at level $P < 0.05$ between means of post-test (analysed by t de Student). NR: non-responders. OR: odds ratios.

Pre-post changes, body composition

The HIT group exhibited a reduced body mass (-1.2 ± 7 kg, $P<0.05$), waist circumference (-4.8 ± 6.1 cm, $P<0.05$), tricipital (-4.8 ± 2.9 mm, $P<0.05$), supra-iliac (-4.7 ± 4.4 mm, $P<0.05$), abdominal (-11.3 ± 4.3 mm, $P<0.05$) skinfold thicknesses, and fat mass ($-5.6 \pm 6.2\%$, $P<0.05$) (Table 2). The RT group exhibited a reduced waist circumference (-3.0 ± 10.9 cm, $P<0.05$) and tricipital (-3.1 ± 5.0 mm, $P<0.05$), supra-iliac (-4.1 ± 5.6 mm, $P<0.05$), and abdominal (13.0 ± 5.1 mm, $P<0.05$) skinfold thicknesses (Table 2). Additionally, there was a significant reduction in fat mass in HIT, as well as an increase in the muscle mass in the RT group (Figure 2).

Table 2. Characteristics of the subjects before and after the 12-week follow-up.

Variable			<i>P</i> value [†]			<i>P</i> value [†]	<i>P</i> value [†]	<i>P</i> value [§]
	HIT Baseline	HIT 12 weeks	HIT 0-12 weeks	RT Baseline	RT 12 weeks	RT 0-12 weeks	HIT vs. RT Baseline	HIT vs. RT 0-12 weeks
Age (y)	34 ± 6			33 ± 7				
Time elapsed from diagnosis (m)	1-3			1-3				
Body composition/anthropometry								
Height (m)	1.56 ± 0.04			1.59 ± 0.05			<i>P</i> =0.145	
Body mass (kg)	74.3 ± 7.3	73.1 ± 6.8	<i>P</i> =0.038	75.6 ± 12.8	75.5 ± 12.2	<i>P</i> =0.345	<i>P</i> =0.125	<i>P</i> =0.789
Body mass index (kg/m ²)	30.5 ± 3.0	30.3 ± 3.0	<i>P</i> =0.789	29.4 ± 4.4	29.6 ± 4.1	<i>P</i> =0.688	<i>P</i> =0.133	<i>P</i> =0.871
Waist circumference (cm)	102.6 ± 6.2	97.8 ± 6.1	<i>P</i> <0.0001	100.4 ± 11.6	97.4 ± 10.3	<i>P</i> <0.001	<i>P</i> =0.110	<i>P</i> =0.377
Tricipital skinfold (mm)	25.5 ± 3.2	20.7 ± 2.6	<i>P</i> <0.0001	26.5 ± 5.5	23.4 ± 4.6	<i>P</i> <0.0001	<i>P</i> =0.567	<i>P</i> <0.001
Supra-iliac skinfold (mm)	32.2 ± 4.7	27.5 ± 4.1	<i>P</i> <0.0001	31.1 ± 5.4	27.0 ± 5.8	<i>P</i> <0.0001	<i>P</i> =0.278	<i>P</i> =0.562
Abdominal skinfold (mm)	40.7 ± 3.6	29.4 ± 5.1	<i>P</i> <0.0001	40.1 ± 3.7	27.1 ± 6.6	<i>P</i> <0.0001	<i>P</i> =0.356	<i>P</i> <0.001
Fat mass (%)	41.2 ± 5.7	35.6 ± 6.8	<i>P</i> <0.0001	41.7 ± 5.5	40.0 ± 5.5	<i>P</i> =0.089	<i>P</i> =0.311	<i>P</i> <0.0001
Muscle mass (%)	23.6 ± 1.7	23.4 ± 1.4	<i>P</i> =0.294	23.2 ± 2.1	24.4 ± 1.8	<i>P</i> <0.001	<i>P</i> =0.621	<i>P</i> <0.0001
Cardiovascular								
Heart rate rest (beats/min)	83 ± 7	80 ± 6	<i>P</i> =0.023	83 ± 8	83 ± 7	<i>P</i> =0.876	<i>P</i> =0.743	<i>P</i> <0.001
Systolic blood pressure (mmHg)	131 ± 4	125 ± 7	<i>P</i> <0.001	126 ± 7	122 ± 5	<i>P</i> <0.001	<i>P</i> =0.066	<i>P</i> <0.001
Diastolic blood pressure (mmHg)	80 ± 7	77 ± 8	<i>P</i> =0.042	75 ± 5 ‡	75 ± 4	<i>P</i> =0.344	<i>P</i> <0.0001	<i>P</i> =0.731
Metabolic/plasmatic								
Fasting glucose (mg/dL)	105 ± 5	98 ± 9	<i>P</i> <0.001	103 ± 7	97 ± 7	<i>P</i> <0.001	<i>P</i> =0.212	<i>P</i> =0.356
Fasting insulin (μU/dL)	16.5 ± 4.6	8.7 ± 3.3	<i>P</i> <0.0001	18.1 ± 4.9	11.2 ± 3.9	<i>P</i> <0.0001	<i>P</i> =0.128	<i>P</i> =0.177
HOMA-IR	4.2 ± 1.1	2.1 ± 0.7	<i>P</i> <0.0001	4.4 ± 1.0	2.8 ± 1.0	<i>P</i> <0.0001	<i>P</i> =0.111	<i>P</i> =0.199
Muscle performance								
1RM _{BC} (kg)	13 ± 7	14 ± 6	<i>P</i> =0.949	15 ± 5	21 ± 7	<i>P</i> <0.001	<i>P</i> =0.088	<i>P</i> <0.001
1RM _{LE} (kg)	34 ± 6	36 ± 9	<i>P</i> =0.345	32 ± 4	45 ± 4	<i>P</i> <0.0001	<i>P</i> =0.139	<i>P</i> <0.001

Prevalence of non-responders by mode of training in insulin resistance

1RM _{SP} (kg)	24 ± 3	25 ± 3	<i>P</i> =0.545	23 ± 4	33 ± 5	<i>P</i><0.0001	<i>P</i> =0.231	<i>P</i><0.0001
1RM _{UR} (kg)	32 ± 8	35 ± 6	<i>P</i> =0.652	31 ± 6	37 ± 5	<i>P</i><0.0001	<i>P</i> =0.239	<i>P</i><0.0001
Endurance performance								
2KMWT (min.s)	21.5 ± 1.1	19.5 ± 1.1 **	<i>P</i><0.0001	22.0 ± 1.0	20.0 ± 1.1	<i>P</i><0.0001	<i>P</i> =0.278	<i>P</i> =0.341

HIT: high-intensity interval training group; RT: resistant training group; Δ%: delta percent pre-post changes; ES: effect size; 1RM_{BC}: one maximum repetition strength test of biceps curl; 1RM_{LE}: one maximum repetition of leg-extension; 1RM_{SP}: one maximum repetition of shoulder-press; 1RM_{UR}: one maximum repetition of upper row; 2KMWT: 2-km walking test. Asterisk denotes significant pre-post changes intra-group. [†] Analysed by Repeated Measures group x time. [‡] Analysed by ANOVA one-way. [§] Analysed by Bonferroni *post hoc*. Bold values denotes significant differences at each pvalue respectively.

Pre-post changes, cardiovascular

HIT group exhibited a reduced heart rate at rest (-3 ± 7 beats/min, $P<0.05$), systolic (-6 ± 7 mmHg, $P<0.05$) (Table 2). The RT group exhibited a reduced systolic blood pressure (-4 ± 6 mmHg, $P<0.05$) during follow-up (Table 2). The HIT group showed a reduced diastolic (-3 ± 7 mmHg, $P<0.05$) blood pressure (Figure 3).

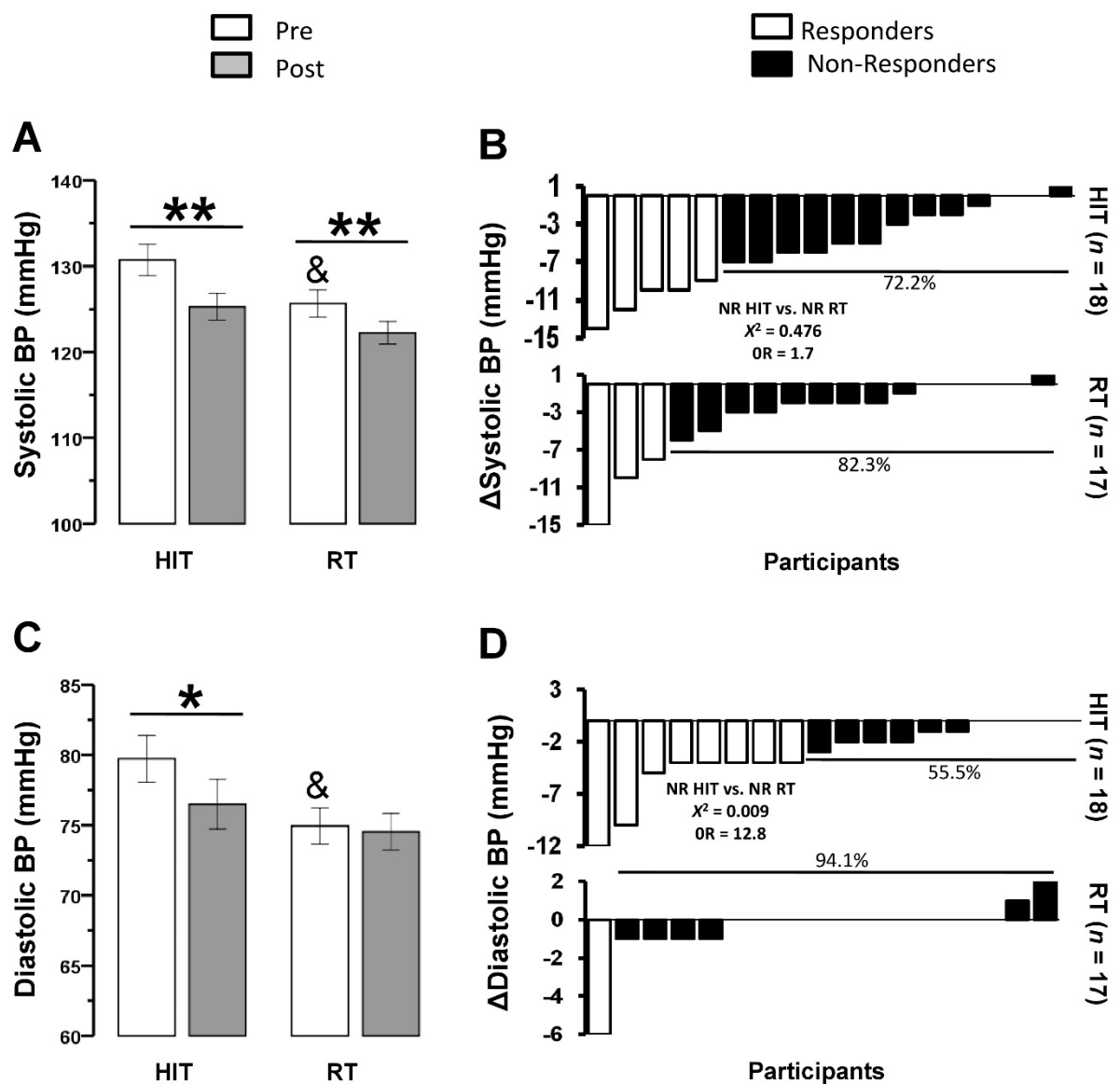


Figure 3. Average changes and non-responder prevalence to decrease systolic (A, B), and diastolic (B, C) blood pressure after 12-weeks of HIT or RT in IR adult woman. HIT: high-intensity interval training group. RT: resistant training group. * Significant difference from baseline within group at level $P<0.01$. **Significant difference from baseline within group at level $P<0.001$. & Significant difference vs HIT group at level $P<0.05$ between means of pre-test (analysed by t de Student). NR: non-responders. OR: odds ratios.

Pre-post changes, metabolic

HIT group exhibited a reduced fasting glucose (-7 ± 7 mg/dL, $P<0.05$), fasting insulin (-7.8 ± 1.3 μ U/dL, $P<0.05$), and HOMA-IR (-2.1 ± 0.4 , $P<0.05$) after intervention, (Table 1). The RT group exhibited a reduced fasting glucose (-6 ± 7 mg/dL, $P<0.05$), fasting insulin (-6.9 ± 4.4 μ U/dL, $P<0.05$), and HOMA-IR (-1.6 ± 1.0 , $P<0.05$) during follow-up (Table 2).

Pre-post changes, strength and endurance performance

The HIT group did not exhibit changes in muscle performance (Table 2). In contrast, RT group exhibited an increased muscle performance in $1RM_{BC}$ ($+6 \pm 6$ kg, $P<0.001$), $1RM_{LE}$ ($+13 \pm 4$ kg, $P<0.0001$), $1RM_{SP}$ ($+10 \pm 4$ kg, $P<0.0001$), and $1RM_{UR}$ ($+6 \pm 5$ kg, $P<0.0001$) during follow-up (Table 2). Both HIT and RT groups exhibited a significant decrease in the time performing the 2KMWT (-2.0 ± 1.1 min, $P<0.001$, and -2.0 ± 1.0 min, $P<0.001$, respectively) during follow-up (Table 2).

NR prevalence to body composition, cardiovascular, and performance co-variables

Significant differences in the NR prevalence between the HIT and RT groups were identified for a decrease in body mass (HIT 33.3% vs. RT 76.5%, $P<0.010$), BMI (HIT 55.6% vs. RT 88.1%, $P=0.032$) (Table 3), and fat mass (HIT 33.3% vs. RT 70.6%, $P=0.028$) (Figure 2). Similar differences were found to an increase in muscle mass (HIT 100% vs. RT 52.9%, $P<0.0001$), and to a decrease in diastolic BP (HIT 55.6% vs. RT 52.9, $P=0.009$) (Figure 2). Other NR differences were found to an increase in $1RM_{BC}$ (HIT 72.2% vs. RT 0%, $P<0.0001$), $1RM_{LE}$ (HIT 72.2% vs. RT 0%, $P<0.0001$), $1RM_{SP}$ (HIT 100% vs. RT 17.6%, $P<0.0001$), and to a decrease in 2KMWT (HIT 11.2% vs. RT 47.1%, $P<0.010$) during follow-up (Table 3).

NR prevalence to glucose control variables

For fasting glucose, fasting insulin, and HOMA-IR, there were no significant differences in the NR prevalence between the HIT and RT groups when NR were detected (Figure 3). No adverse events were reported over the course of this investigation. The average exercise-training days and total exercise time during the program were 31 ± 6 days and 3534 ± 684 minutes in the HIT group and 30 ± 7 days and 3240 ± 756 minutes, respectively, in the RT group with no difference between the groups.

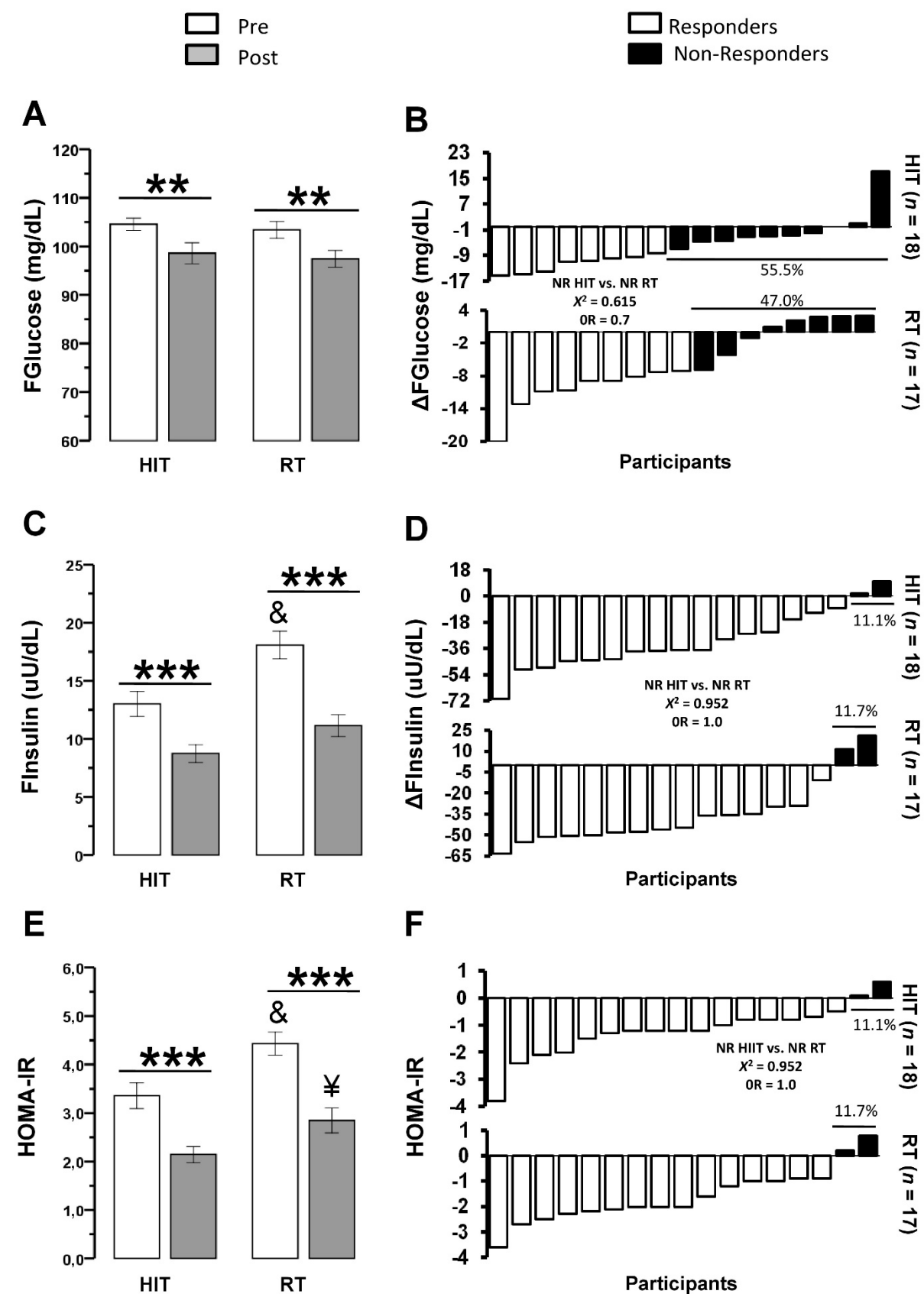


Figure 4. Average changes and non-responder prevalence to decrease fasting glucose (A, B), fasting insulin (C, D), and HOMA-IR (E, F) after 12-weeks of HIT or RT in insulin resistant adult woman. HIT: high-intensity interval training group. RT: resistant training group. FGlucose: fasting glucose, FInsulin: fasting insulin, HOMA-IR: homeostasis model assessment of insulin resistance. **Significant difference from baseline within group at level $P<0.001$. *** Significant difference from baseline within group at level $P<0.0001$. & Significant difference vs HIT group at level $P<0.05$ between means of pre-test (analysed by t de Student). ¥ Significant difference vs HIT group at level $P<0.05$ between means of post test (analysed by t de Student). R: non-responders. OR: odds ratios.

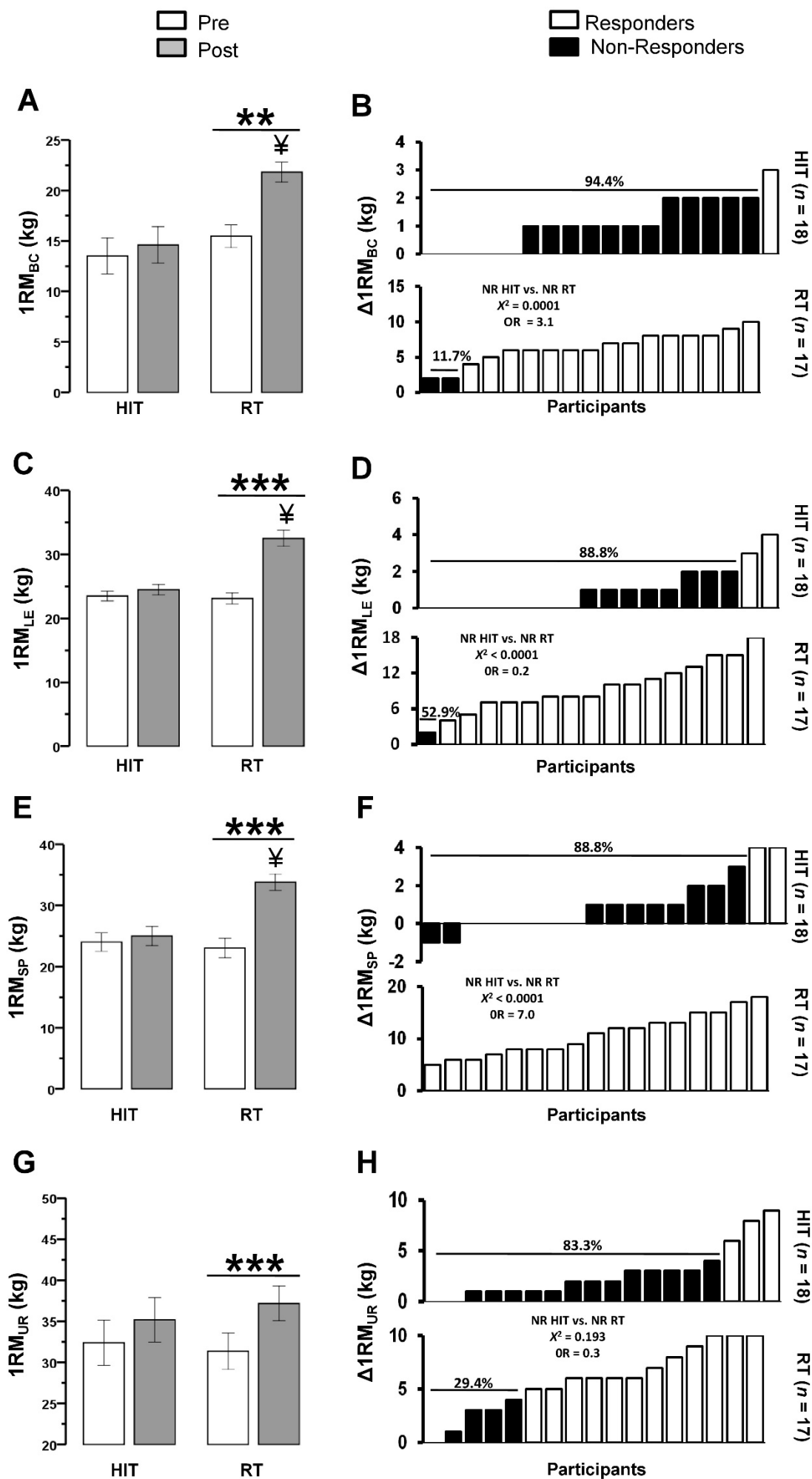


Figure 5. Average changes and non-responder prevalence to improve the strength in biceps curl (A, B), leg extension (C, D), shoulder press (E, F), and upper row after 12-weeks of HIT or RT in insulin resistant adult woman. HIT: high-intensity interval training group. RT: resistant training group. **Significant difference from baseline within group at level $P < 0.001$. *** Significant difference from baseline within group at level $P < 0.0001$. ≠ Significant difference vs HIT group at level $P < 0.05$ between means of post test (analysed by t de Student). R: non-responders. OR: odds ratios.

Discussion

The major novel finding of the present study is that both the HIT and RT programs were similarly effective in reducing the fasting glucose, insulin, and HOMA-IR, and there were no differences in the NR prevalence between the HIT and RT after 12-week of follow-up in IR sedentary women. Furthermore, we identified significant differences in the NR prevalence between the groups in other body composition, cardiovascular, and performance co-variables included in which the mode of training played a determinant role. These data show that supervised exercise programs of HIT/RT are a practical alternative for IR sedentary women for improving cardiometabolic and muscle health. To our knowledge, this study represents the first randomized clinical trial that evaluates NR prevalence after training testing with different protocol of training.

The evidence for HIT improving cardiometabolic risk factors in T2DM is not trivial (C. Alvarez et al., 2016; Gillen et al., 2016; Holten et al., 2004; Little et al., 2011; Shaban et al., 2014). Thus, it is noteworthy that 2-weeks (Shaban et al., 2014) or 16-weeks of HIT have resulted in mean absolute reductions in 24-h glucose concentrations of -13.1 (Little et al., 2011) and a -14.3% in fasting glucose (C. Alvarez et al., 2016) in T2DM subjects. After 12-weeks of HIT or RT in the current study, we identified decreases in the fasting glucose of -6.6 and -5.8%, respectively, which is consistent with the literature. Two-weeks of HIT also decreased HOMA-IR -9.5% in adult men (Gillen et al., 2016). The mechanisms involved in the effects of HIT are not understood; however, increases in insulin sensitivity may explain an increase in the peripheral glucose disposal, which likely increases the Glut-4 protein content and mitochondrial capacity (Little et al., 2011); these changes may increase fat oxidation and clarify the molecular protein signals interrupted by the intramyocellular fat. However, 6-weeks of RT was similarly effective at decreasing the fasting glucose by -3.6% and glycated hemoglobin by -2.6% in T2DM subjects (Holten et al., 2004).

The NR prevalence has predominately been investigated in terms of endurance training (Boulé et al., 2005; Yates et al., 2013) in contrast to HIT (Astorino & Schubert, 2014; Higgins et al., 2015) or RT (Churchward-Venne et al., 2015; Fisher, Bickel, & Hunter, 2014; Moker et al., 2014; Winett et al., 2014); however, both approaches are regular training modes used in populations with low glucose control and cardiometabolic risk factors. For example, 12-weeks of RT (2 days/week, 2 exercises, at maximal effort) resulted in 44% NR to an improvement in the OGTT in prediabetic subjects (Winett et al., 2014). Prehypertensive subjects exhibited a NR prevalence between 6.6 and 9.4% to a decrease in fasting glucose in adult subjects after 20-weeks of RT (Moker et al., 2014).

Consistent with this finding, when T2DM subjects were under RT or concurrent training, there was a 21% NR to a decrease in glycated hemoglobin, fat mass, BMI, and molecular protein markers of skeletal muscle (N. A. Stephens et al., 2015). After 12- and 24-weeks of RT, there was a NR prevalence of 4.5 and 23% to a decrease in body mass, and to an increase in the $1RM_{LE}$ of 0.9% and 1.17% to each volume, respectively. In this previous study, it is highlighted that there are variables that may be volume-dependent, whereas other variables, such as strength performance, are not volume-dependent to elicit a greater/lower percentage of NR to 12- or 24-weeks of training (Churchward-Venne et al., 2015). We identified a 5.5% (1 case) prevalence of NR in HIT and a 0% (0 cases) prevalence of NR in RT after intervention for fasting glucose.

One characteristic of NR typically includes no change or a worsened response; for example, after RT combined with endurance training in older female adults, there was a 40% NR described, as all of those subjects by contrast increased fat mass, decreased fat-free mass, and increased inflammatory markers such as tumor necrosis factor alpha and c reactive protein (Fisher et al., 2014). However, considering other HIT interventions, after 6-weeks of HIT in young adults, 50% were reported as NR to an improvement in the area under the curve of glucose in the OGTT (Higgins et al., 2015). Moreover, although we are unable to make comparisons, when a large sample of 1.687 subjects underwent endurance training (30-50 min/session, 3 days/week, 20-weeks), there was a NR prevalence to a decrease in fasting insulin of 8.4% (NR reported as adverse response by the 2 TE criteria) (Claude Bouchard et al., 2012), being these results similar to our findings of NR to decrease fasting insulin in both HIT 5.5%, and RT group 11.7%. When an insulin sensitivity index was included in 600 subjects, after 20-weeks of endurance training (30-50 min/session, 3 days/week, 20-weeks), one study identified a 42% NR incidence to an improvement (increase) in this marker of glucose control (Boulé et al., 2005). In the same profile of subjects, after 20-weeks of endurance training, other authors have reported that an increase in physical activity per week plus an education component in glucose control topics resulted in an NR prevalence of 3% to a decrease in fasting glucose (reported as adverse responders by the similar 2 TE criteria classification) (Yates et al., 2013).

Although they were not the central topic, significant changes were identified in other anthropometric, cardiovascular, and performance co-variables. In accordance, nine months of RT, including diet intervention, resulted in incidence prevalence of 7.2% NR to a decrease in waist circumference and 8.6% NR to a decrease in total fat mass (Gremeaux et al., 2012). After 16-weeks of RT, 50% of older adult participants categorized as NR exhibited a decreased fat-free mass, an increased percentage of fat, and an more alterations in inflammation markers (Fisher et al., 2014).

For example, after 2- or 12-weeks of HIT, there were clear differences in the NR prevalence to increase the fat oxidation with 30% and 10% on NR, respectively in each volume of training, which indicates that in the same variables, the volume of training does not necessarily play a key role (Astorino & Schubert, 2014). We also demonstrated that systolic blood pressure was decreased after both programs by -4.5 in HIT and -3.1% in RT, as well as heart rate at rest by -3.6% in this group; the diastolic blood pressure was decreased only in HIT by -3.7% (Figure 2). Likewise, when Paoli et al applied 12-weeks of an endurance, high-intensity of RT plus endurance, or low-intensity of RT plus endurance training, they found a reduction of diastolic blood pressure of -6 mmHg, and a minor reduction in the endurance -3, as well as the low intensity RT plus endurance group -2 mmHg. Interestingly, these results were displayed with additional decreases in fat mass -17.4%, that were more pronounced than the low-intensity RT plus endurance -9.6%, and the endurance group -5% (Paoli et al., 2013). A recent meta-analysis indicated that a single 90-min session of RT decreased systolic blood pressure by -5.3 mmHg (-8.5 to -2.1, CI 95%) for up to 24h (Casonatto, Goessler, Cornelissen, Cardoso, & Polito, 2016), although considering that this is a long time to the real availability of the population, we presume that short but high-intensity RT stimuli can be able to support more benefits from RT than low-intensity protocols.

On the other hand, it has been suggested that HIT has more power considering all cardiovascular parameters assessed, where the angiogenic mechanisms could be related (Gustafsson, Puntchart, Kaijser, Jansson, & Sundberg, 1999). For example, after 16-weeks of a mode of HIT, there was a reduction of -1.7% in systolic and a reduction of -2.8% in diastolic blood pressure during 24 h of monitoring (Emmanuel G. Ciolac et al., 2010). Including 5 HIT-studies (Gurd et al., 2015) demonstrated 22% NR prevalence to an increased endurance performance by the maximum oxygen uptake ($\text{VO}_{2\text{max}}$). In this study, the authors indicated an advantage of training more versus less frequently (4 versus 3 times per week) because there was 0% NR to an increase in the $\text{Vo}_{2\text{max}}$, which suggests that the frequency may be a factor that influences the NR.

Considering the sedentary lifestyle of the population, IR and the risk for T2DM are increasing. The knowledge of a more effective mode of training (i.e., training modes as endurance, HIT, RT, or other protocols that achieve a reduced amount of NR prevalence after training interventions), in accordance with the profile of individuals (i.e., IR subjects, healthy individuals, or athletes) and achievement of improvements in their risk factors for T2DM may be useful information for practitioners, public health exercise programs, and populations with/at risk of T2DM. This may positively affect disease morbidity, mortality (Zhang et al., 2010) and health care expenditures (Shaw et al., 2010).

HIT and RT programs have resulted in glycemic control improvements (HIT: fasting glucose -6.6%, insulin -47.2%, and HOMA-IR -50%; and RT: fasting glucose -5.8%, insulin -38.1, and HOMA-IR -36.3), similar to increased volumes of exercise (> 150 min/week) (Umpierre et al., 2011). Thus, because most T2DM patients are sedentary and physically inactive and considering that a lack of time is the most cited barrier to regular exercise participation (Troost, Owen, Bauman, Sallis, & Brown, 2002), these findings may have important implications for public health. Moreover, decreases of 2.1/0.9 mmHg in systolic/diastolic blood pressure reduced major cardiovascular events by 10% in T2DM subjects (Turnbull et al., 2005). We demonstrated that HIT-induced improvements occurred in systolic blood pressure of -6 mmHg compared with -4 mmHg in the RT group; thus, our findings may have important clinical implications. Furthermore, following a recent diagnosis of IR, patients must have 6-months to change their lifestyle without pharmacological medication; in the present study, decreases of -50 to -38% in the HOMA-IR were identified after HIT and RT, which thus has clinical implications.

Moreover, the HIT program resulted in no cases of NR subjects in the body composition co-variable waist circumference, and showed more power effects decreasing body mass, waist circumference, tricipital, supra-iliac, and abdominal skinfold, as well as fat mass; thus, HIT is a recommended mode of training to elicit a reduced prevalence of NR after 12-weeks of training, including 3 times/week, a total time commitment per week of 114 min, and a volume of work per session of 12 min. In contrast, RT elicited less NR prevalence in body composition abdominal skinfold, and performance variables $1RM_{BC}$, $1RM_{LE}$; thus, this mode of training is similarly recommended to both decrease body fat markers and increase strength.

Strengths and limitations

The strengths of this study included that there was high exercise compliance, data for both training-induced changes, and NR differences between two modes of training at the same time; moreover, we also report glucose control and other body composition, cardiovascular, endurance, and strength performance parameters. One primary limitation in this study was the lack of a true no-exercise control group. Thus, we are unable to determine causality in our interpretation of the exercise-induced improvements in cardiometabolic health parameters. Second, as a common tool to assess body weight and the relevant parameters of body composition, BIA was used in the present study. However, it is not the 'gold standard' in body composition measurement; nevertheless, this was not the central topic of this study. Another limitation is the lack of dietary control during the course of the intervention. To minimize the influence of diet, we continually reminded subjects of their commitment to maintain

their current dietary habits. Future studies may consider tighter control of these factors to ensure that the effects of these different factors are isolated and identified in a relatively longer intervention. An additional limitation is that the 1RM test was evaluated mechanically using the best of three attempts; however, this test was supervised by a professional exercise physiologist.

Conclusions

In summary, short and low volumes of HIT and RT programs applied alone were effective at improving glycemic control, as well as other body composition, cardiovascular, endurance and strength performance parameters. There were no differences in the NR prevalence between HIT and RT after 12-weeks of follow-up in the main glucose control variables; however, there were significant differences in the body composition BMI co-variable in which the mode of training played a role. These findings were obtained with a weekly time commitment that was 24% to 28% lower than the minimal recommendations in the current guidelines (S. R. Colberg et al., 2010).

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Chapter 3

Prevalence of non-responders for glucose control markers after 10-weeks of high-intensity interval training in adult women with higher and lower insulin resistance

***Cristian Álvarez,** Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez and Mikel Izquierdo. Prevalence of Non-responders for Glucose Control Markers after 10 Weeks of High-Intensity Interval Training in Adult Women with Higher and Lower Insulin Resistance. *Frontiers in physiology* 2017;(8):479.

Prevalence of non-responders for glucose control markers after 10-weeks of high-intensity interval training in adult women with higher and lower insulin resistance

Abstract

Background/aims: This study assessed the effects of HIT and the prevalence of NR in adult women with higher and lower levels of IR. **Methods:** Forty adult women were assigned to a HIT program, and after training were analysed in two groups; a group with higher IR (H-IR, 40 \pm 6 years; BMI: 29.5 \pm 3.7 kg/m²; N = 20) and a group with lower IR (L-IR, 35 \pm 9 years; 27.8 \pm 2.8 kg/m²; N = 20). Body composition, cardiovascular, metabolic and performance variables were measured at baseline and after 10-weeks of training. **Results:** There were significant training-induced changes [Δ percent (1%)] in fasting glucose, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) scores in the H-IR group (−8.8, −26.5, −32.1%, P < 0.0001). There were significant differences in the prevalence of NR between the H-IR and L-IR groups for fasting glucose (25 vs. 95%, P < 0.0001) and fasting insulin (P = 0.025). **Conclusions:** Independent of the ‘magnitude’ of the cardiometabolic disease, no differences were observed in the NR prevalence with regard to improved HOMA-IR or to body composition, cardiovascular, and muscle performance co-variables after 10-weeks of HIT in sedentary adult women.

Keywords: high-intensity interval training, non-responders, insulin resistance, women

Introduction

Exercise training is a strategy for the prevention and treatment of several inactivity-related metabolic diseases, such as IR (Mancilla et al., 2014) and type 2 diabetes mellitus (T2DM) (C. Alvarez et al., 2016). Similarly, exercise interventions, including resistance training, together with pharmacological and dietary interventions, represent the cornerstones of T2DM management (ADA, 2011). In addition to the beneficial effects on glycaemic control (Umpierre, Ribeiro, Schaan, & Ribeiro, 2013) and other risk factors of T2DM (Chudyk & Petrella, 2011; Figueira et al., 2014), physical exercise is effective in improving muscle strength (Dunstan et al., 2002), cardiovascular function (Cano-Montoya et al., 2016), and functional capacity (Cadore & Izquierdo, 2015). In this regard, combined resistance and endurance training is an effective intervention to promote overall physical fitness in T2DM patients (Balducci et al., 2012). More recently, HIT (i.e., repeated short bursts of high intensity efforts with rest breaks in between each bout of exercise) has emerged as a time-efficient exercise modality to continuous traditional endurance exercise training to improve cardiometabolic health (Ramírez-Vélez, Hernandez, et al., 2016).

However, despite the frequent reports of ‘mean’ exercise-related changes, there is wide inter-individual variability in the results of exercise training (Astorino & Schubert, 2014). Under the same stimulus, some subjects, termed responders (R), achieve benefits after training, while others, termed non-responders (NR), show an unchanged or worsened response (Sisson et al., 2009). In the literature, this phenomenon has been characterized using several terms, such as low/high responders (Davidsen et al., 2011), non-responders/responders (Sisson et al., 2009), or adverse response (Claude Bouchard et al., 2012). Genetic (N. A. Stephens et al., 2015) and environmental factors (C. Bouchard & Rankinen, 2001a) have been suggested to be responsible for this variability, although not all of the potential environmental factors (e.g., different health status, different mode of exercise training) have been explored.

Furthermore, the prevalence of these unchanged or worsened responses (i.e., percentage of subjects who do not improve/show a worsened response with regard to a variable), known as NR prevalence, has been reported predominantly after endurance (Claude Bouchard et al., 2012; Sisson et al., 2009) and resistance training (Churchward-Venne et al., 2015; Moker et al., 2014). There have been no studies reporting the NR prevalence associated with risk factors for T2DM after HIT, which improves body composition, cardiovascular, plasma, and performance variables in different cohorts (C. Alvarez et al., 2016; Astorino & Schubert, 2014).

For example, in one study of IR adult women after 8-weeks of HIT, there were reductions of 12 to 14% in fasting glucose, 27 to 37% in fasting insulin and ~40% in homeostasis model assessment of insulin resistance (HOMA-IR) (C. Álvarez, Ramírez-Campillo, R, Henríquez-Olguín, C, Castro-Sepúlveda, M, Carrasco, V, Martínez C., 2014). In another study of T2DM subjects after 16-weeks of HIT, there was a decrease of ~14% in fasting glucose, with additional decreases of ~4 mmHg in blood pressure, ~2% in body mass, ~4% in waist circumference and ~19% in subcutaneous fat (C. Alvarez et al., 2016). Notably, another study showed that only 2-weeks of HIT decreased the average 24-h fasting glucose by approximately 13% (Little et al., 2011). Finally, a study of subjects with poor glucose control showed an improvement (-12%) in the area under the curve of the oral glucose tolerance test (OGTT) and a -4.2 kg decrease in fat mass after 12-weeks of HIT (Mancilla et al., 2014).

Latin America has experienced an epidemiological transition characterized by an increasing burden of cardiometabolic disease from physical inactivity and shifts in diet and lifestyle patterns (Rivera et al., 2014). Evidence in Chilean adults suggests similar associations between low physical activity levels and cardiometabolic risk factors and between health status and overweight/obesity (Vio, Albala, & Kain, 2008). Thus, the aim of the present study was to assess the effects and NR prevalence (as indicated by glucose control variables) after 10-weeks of HIT in IR and healthy women. A second aim was to assess other body composition, cardiovascular, and performance variables. We hypothesized that independent of health status, there would be no difference in the NR prevalence (i.e., percentage of NR cases after exercise) for changes to glucose control variables after HIT between IR and metabolic-healthy women by using the HOMA-IR criteria.

Material and methods

Participants and study design

The first stage of the study was to recruit, using a short telephone survey, adult patients who were previously identified in their last clinical exam as at risk of T2DM and who had dropped out from their regular appointments at the healthcare center. In this first stage, 168 sedentary adult women (aged ≥ 18 years) with no background of regular exercise training volunteered to be screened for IR or metabolic-healthy status using the HOMA-IR based on the measurement of both fasting glucose and fasting insulin plasmatic markers. After this first screening, 65 individuals classified as 'insulin-resistant' ($N = 65$) were excluded for multiple reasons (16 due to age > 40 years; 2 due to being recently physically active; 5 due to diagnosis with hypertension; 5 due to diagnosis with T2DM; 5 due to diagnosis with hypothyroidism; 3 due to musculoskeletal injury; 21 due to no T2DM history; 6 due to stationary asthma/respiratory disease; and 7 due to having an address in a rural area). Similarly, 25 subjects identified as 'healthy' ($N = 25$) were also excluded for similar reasons (6 due to age ≥ 40 years; 12 due to being physically active; 2 due to diagnosis with hypothyroidism; and 5 due to having an address in a rural area). Finally, 78 screened subjects ($N = 78$) were assigned to two different groups according to their health status: After the follow-up, the final sample included in the statistical analysis was to HIT insulin-resistant group (HIT-IR, $N = 20$) and to the HIT metabolic-healthy control group (HIT-CON, $N = 20$). None of the subjects were taking oral hypoglycaemic medications to improve metabolic control of glucose because they all had been recently diagnosed with IR by our research team.

All IR and metabolic-healthy subjects participated in the HIT exercise training program to determine the effect of 'health status' on NR prevalence after exercise. The treatment allocation is described in (Figure 1).

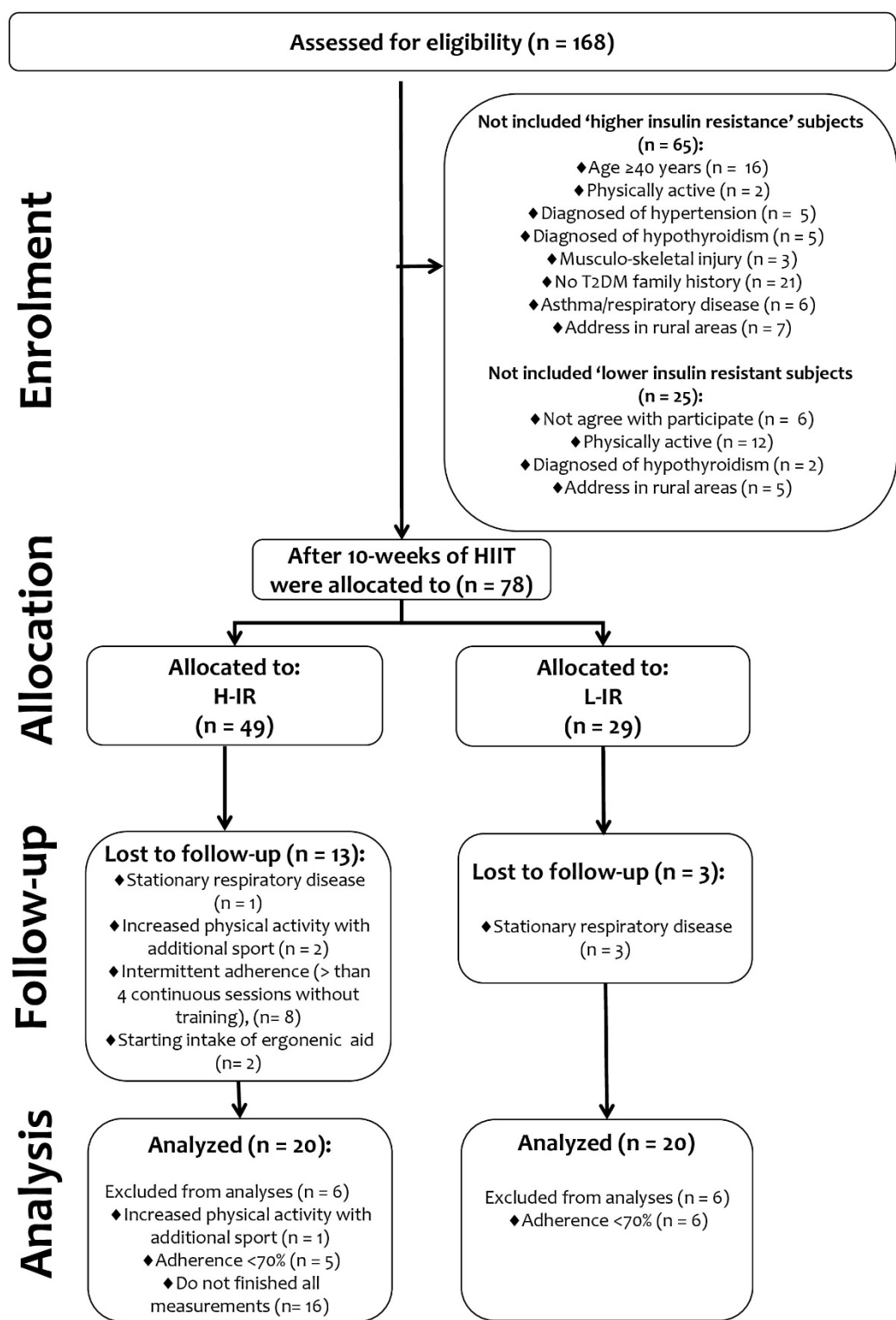


Figure 1. Study design.

All participants were informed about the experimental procedures and about possible risks and benefits associated with participation in the study. Informed consent was obtained before any of the assessments were performed. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board for the use of human subjects of the local Ethics Committee of the University of los Lagos (Comité de Revisión Científica y Etica Institucional del Departamento de Ciencias de la Actividad Física de la Universidad de Los Lagos). Characteristics of the study participants are provided in (Table 1 and Table 2).

Table 1. Body composition characteristics before and after 10-weeks of high-intensity interval training in a higher (H-IR), and lower insulin resistance adult women group (L-IR).

	H-IR Baseline	H-IR 10-weeks	L-IR Baseline	L-IR 10-weeks	Pvalue†		Pvalue†		Pvalue‡	Pvalue§
					H-IR pre-post	Δ% (ES)	L-IR pre-post	Δ% (ES)	H-IR vs. L-IR Baseline	H-IR vs. L-IR Post
Body composition										
N =	20		20							
Age (y)	40 ± 6		35 ± 9							
Height (cm)	155 ± 0.04		158 ± 0.05							
Body mass (kg)	71.4 ± 9.4	69.1 ± 9.1	70.0 ± 7.3	67.8 ± 7.7	P=0.089	-3.2 (-0.23#)	P=0.061	-3.1 (-0.29#)	P=0.603	P=0.397
Body mass index (kg/m²)	29.5 ± 3.7	28.6 ± 3.5	27.8 ± 2.8	27.0 ± 3.0	P=0.067	-3.0 (-0.24#)	P=0.189	-2.8 (-0.31#)	P=0.112	P=0.365
Waist circumference (cm)	98.8 ± 8.2	93.6 ± 8.0	99.7 ± 7.1	95.9 ± 6.7	P<0.010	-5.2 (-0.61&)	P=0.046	-3.8 (-0.52#)	P=0.719	P=0.167
Tricipital skinfold (mm)	24.7 ± 7.2	21.4 ± 6.9	24.1 ± 6.3	20.8 ± 6.1	P<0.010	-13.3 (-0.48#)	P<0.0001	-13.6 (-0.57#)	P=0.772	P=0.399
Supra-iliac skinfold (mm)	31.4 ± 6.4	25.3 ± 7.3	33.7 ± 7.6	29.1 ± 8.1	P<0.0001	-19.4 (-0.83&)	P<0.0001	-13.6 (-0.55#)	P=0.309	P=0.112
Abdominal skinfold (mm)	40.5 ± 12.1	33.1 ± 9.4	33.2 ± 7.4	28.0 ± 6.0	P<0.0001	-18.2 (-0.65&)	P<0.010	-15.6 (-0.85&)	P=0.028	P=0.126

Data are means and ± SD; Delta changes (Δ%) = [10-weeks * 100 / baseline]. ES: effect size. † Analysed by Repeated Measures group x time. ‡ Analysed by ANOVA one-way. § Analysed by Bonferroni post hoc. # Indicates 'small' standardized ES at level $P \leq 0.05$. &Indicates 'moderate' standardized ES at level $P \leq 0.05$

Table 2. Cardiovascular, plasmatic, and performance characteristics of the subjects before and after 10-weeks of high-intensity interval training in insulin resistance (H-IR), and after high-intensity interval training control group (L-IR).

	H-IR Baseline	H-IR 10-weeks	L-IR Baseline	L-IR 10-weeks	Pvalue†		Pvalue†		Pvalue‡	Pvalue§
					H-IR pre-post	Δ% (ES)	L-IR Pre-post	Δ% (ES)	H-IR vs. L-IR Baseline	H-IR vs. L-IR Post
N =	20		20							
Cardiovascular										
Systolic blood pressure (mmHg)	127 ± 4	124 ± 3	125 ± 4	121 ± 4	P=0.059	-2.3 (-1.09&)	P<0.010	-3.2 (-0.95&)	P=0.065	P=0.134
Diastolic blood pressure (mmHg)	74 ± 6	73 ± 6	72 ± 4	71 ± 4	P=0.076	-1.3 (-0.29#)	P=0.070	-1.3 (-0.16#)	P=0.083	P=0.377
Metabolic/plasmatic										
Fasting glucose (mg/dL)	113 ± 7	103 ± 6	93 ± 4	91 ± 5	P<0.0001	-8.8 (-1.65¶)	P=0.179	-2.1 (-0.50#)	P<0.0001	P<0.0001
Fasting insulin (µU/dL)	20.0 ± 4.7	14.7 ± 6.6	12.4 ± 2.7	10.8 ± 2.8	P<0.0001	-26.5 (-1.06&)	P=0.145	-12.9 (-0.57#)	P<0.0001	P<0.0001
HOMA-IR	5.6 ± 1.6	3.8 ± 2.0	2.9 ± 0.7	2.4 ± 0.7	P<0.0001	-32.1 (-1.23¶)	P=0.165	-17.2 (-0.62&)	P<0.0001	P<0.0001
Strength performance										
1RM _{LE} (kg)	31 ± 3	35 ± 5	34 ± 4	39 ± 4	P<0.010	+12.9 (0.96&)	P=0.045	+14.7 (1.25¶)	P=0.068	P=0.211
1RM _{UR} (kg)	23 ± 3	25 ± 2	22 ± 2	24 ± 3	P=0.078	+8.6 (0.62&)	P=0.067	+9.0 (0.44#)	P=0.193	P=0.267

Data are means and ± SD; Delta changes (Δ%) = [10-weeks * 100 / baseline]; HOMA-IR: homeostasis model assessment of insulin resistance; 1RM_{LE}: one-maximum repetition of leg extension; 1RM_{UR}: one-maximum repetition of upper row. † Analysed by Repeated Measures group x time. ‡ Analysed by ANOVA one-way/or ANCOVA § Analysed by Bonferroni post hoc. # Indicates 'small' standardized ES at level P≤0.05. &Indicates 'moderate' standardized ES at level P≤0.05. ¶ Indicates 'large' standardized ES at level P≤0.05.

Eligibility criteria included the following: a) diagnosed with IR by the plasma HOMA-IR marker using a cut-off point of HOMA-IR ≥ 2.6 for the diagnosis of IR in the Chilean population (Garmendia, Lera, Sánchez, Uauy, & Albala, 2009), b) physical inactivity (volume of ≤ 150 min/week of low-moderate physical activity or < 75 min/week of vigorous physical activity) (G. O'Donovan et al., 2010), c) no familial (parents/siblings) history of T2DM, d) living only in urban areas, and e) under the public Chilean healthcare system (i.e., not the private health system). Exclusion criteria included participants with the following: a) potential medical or musculoskeletal problems, b) osteoarthritis, c) history of ischemic disease, d) arrhythmia, e) asthma, f) chronic obstructive pulmonary disease, and g) utilization of drugs that modulate metabolic or respiratory control.

Responder (R) and non-responder (NR) criteria classification

Using previous criteria applied in exercise interventions (Bonafiglia et al., 2016), the inter-individual variability to exercise training of the subjects were categorized as responders (R), and non-responders (NR) using the typical error measurement (TE). Thus, the TE was calculated for the main outcome of HOMA-IR, as well as to the other plasmatic (fasting glucose, fasting insulin), body composition, cardiovascular and performance co-variables included. The TE was calculated for the main outcomes (fasting glucose, fasting insulin and HOMA-IR), as well as to the other co-variables as described previously (Will G. Hopkins, 2000) using the following equation:

$$TE = SD_{diff} / \sqrt{2}$$

Where SD_{diff} is the variance (standard deviation) of the difference scores observed between the 2 repeats of each test. A NR for HOMA-IR, as well as to all the others co-variables included was defined as an individual who failed to demonstrate a decrease or increase (in favour of beneficial changes) that was greater than 2 times the TE away from zero. A change beyond 2 times the TE means that there is a high probability (i.e. 12 to 1 Odds) that this response is a true physiological adaptation beyond what might be expected to result from technical and/or biological variability (Will G. Hopkins, 2000).

Body composition and cardiovascular assessments

Body composition and blood pressure assessments were carried out during the first week of the allocation stage. Body mass was assessed by a digital weight scale with an accuracy of 0.1 kg (Omron HBF-INT™, Omron Healthcare Inc., Lake Forest, L, USA). Height was assessed with a professional stadiometer (Health o Meter™

Professional, Sunbeam Products Inc., Chicago, IL, USA) with an accuracy of 0.1 cm, and BMI was calculated according to the formula (kg/m^2). Waist circumference was assessed with an inextensible measuring tape with 0.1 cm accuracy (HoechstmassTM, Sulzbach, Germany).

Three skinfold measurements of subcutaneous adipose tissue (i.e., tricipital, supra-iliac, and abdominal skinfold) were assessed using a LanguetteTM skinfold calliper (Beta Technology Inc., Santa Cruz, California, USA) according to standard protocols (Marfell-Jones, 2006). The systolic and diastolic blood pressure were assessed by an automatic monitor (Omron HEM 7114TM, Omron Healthcare Inc., Lake Forest, IL, USA), in triplicate (2 min of interval between measurements), and after 15 min of resting with the subjects in seated position following standard classification procedures (Chobanian et al., 2003).

Plasma metabolic markers

The plasmatric measurements were carried out in the 2nd week. Subjects arrived at the laboratory of the Riñihue clinic between 8 and 10 in the morning after a 10-h overnight fast. Blood samples (approximately 3.5 mL) was collected in tubes with specific anticoagulant gels for fasting glucose and fasting insulin measurements at baseline and at the 10-week follow-up. Samples were placed on ice and centrifuged at 4,000 rpm ($1700 \times g$) for 5 minutes at 4°C. Plasma samples were immediately transferred to pre-chilled microtubes and stored at -20 °C for later analysis. Plasma glucose was analysed by enzymatic methods using standard kits (Wiener Lab Inc., Rosario, Argentina) on an automatic analyser (Metrolab 2300 PlusTM, Metrolab Biomed Inc., Buenos Aires, Argentina). Fasting insulin was measured by RIA (DPC, Los Angeles, CA, USA). The HOMA-IR insulin resistance index was calculated using the Matthews equation (Matthews et al., 1985): $\text{HOMA-IR} = [\text{Fasting glucose (mg/dL)} * \text{Fasting insulin (}\mu\text{U/dL)}] / 405$). The same blood sampling and preparation procedure was performed at the end of the 10-week follow-up, 48 h after the last exercise session to avoid possible acute effects of exercise.

Familiarization with the exercise training program

In weeks 3 and 4, in 3 sessions, the subjects of both groups were enrolled in a familiarization period for the HIT protocol, as well as for the 1RM_{LE} and 1RM_{UR} tests. In the first and second sessions, the subjects were educated about the cycling machines and the free weights, as well as the exercise machine for the strength test. In the following 4 sessions, the subjects underwent the HIT.

One-repetition maximum test

In week 5, after de familiarization process with the test and before the intervention, both groups performed the one-repetition maximum strength test for $1RM_{LE}$ and $1RM_{UR}$ as previously described (Izquierdo et al., 2004). The $1RM_{LE}$ test involved an exercise machine (OXFORD™, model EE4002, Santiago, Chile), and in the $1RM_{UR}$ test, free weights with bars were used. In brief, for the $1RM_{LE}$ test, the subjects began by lifting a load with both legs with a weight in the machine. For the $1RM_{UR}$ test, the subject adopted a body angle of 90° of flexion, grabbed a bar with weights and plates, and with both arms extended, reached the bar to almost the knee position. The highest load from three attempts per exercise was reported.

High-intensity interval training exercise program

The HIT was started in the 6th week and was performed 3 times per week, for a total of 30 sessions, using exercise bikes (OXFORD™, model BE2601, OXOFORD Inc., Santiago, Chile). Each participant performed a range of 8 to 12 cycling intervals during the intervention period. The time of each cycling work interval was 60 s, with a rest period of 120 s of passive rest (over the bicycle without movement) between work intervals. This rest period was progressively decreased (2 min weeks 1-2, 1.45 min weeks 3-5, 1.30 min weeks 6-8, and 1.15 min weeks 9-10), reaching a time of 1.15 min in the tenth week. Cycle revolutions were maintained at a range of 50 to 70 rpm and a speed between 20 and 40 km/h during each work interval. Subjects were required to cycle between 8 and 10 points of the modified 0-10 Borg scale during the work interval (Emmanuel Gomes Ciolac et al., 2015). This subjective intensity corresponds to a range of 70 to 100% of the maximum heart rate according to the Karvonen formula (Karvonen, 1988). All subjects had good exercise tolerance, and none of the participants reported an injury. Exercise compliance was $82.0 \pm 3\%$ in the HIT-IR group and $79.3 \pm 4\%$ in the HIT-CON group.

Statistical analysis

Data are presented as the mean \pm standard deviation (SD). Normality and homoscedasticity assumptions for all data were assessed using the Shapiro-Wilk test and Levene's test, respectively. The Wilcoxon test was used for non-parametric data. One-way ANOVA was performed to test differences between baseline groups. An ANCOVA was conducted for variables that were significantly different at baseline. A repeated-measures ANOVA (groups x time) was used to determine differences in all dependent variables between pre- and post-tests using each group x time. To determine differences between R and NR by groups HIT-IR x HIT-CON, the Chi-square

test (χ^2) was used for categorical variables. After the intervention, the TE were calculated for the pre-post changes for each dependent variable. The subjects were categorized as R and NR according to the previously described criteria of 2 TE (Bonafiglia et al., 2016). The Bonferroni *post hoc* test was applied to establish differences among groups. Additionally, Cohen's test was used to detect effect size (ES), with threshold values at 0.20, 0.60, 1.2, and 2.0 for small, moderate, large, and very large effects, respectively (William G. Hopkins, Marshall, Batterham, & Hanin, 2009). ES values are presented as the mean with 95% confidence limits. Odds ratios (OR) were used to assess NR dichotomous variables between groups. All statistical analyses were performed with SPSS statistical software version 18 (SPSSTM Inc., Chicago, Illinois, USA). The alpha level was fixed at ($P \leq 0.05$) for all statistical significance.

Results

Follow-up

Subjects with < 70% training attendance were excluded from all statistical analyses after the intervention; after that exclusion, the characteristics of the analysed sample were as follows: the HIT-IR group (age 40 ± 6 y, $N = 20$) and the HIT-CON group (age 35 ± 9 y, $N = 20$) (Figure 1).

Body composition measurements

At baseline, there were significant ($P \leq 0.05$) differences between groups for abdominal skinfold (Table 1). There were significant ($P \leq 0.05$) pre-post changes (presented as delta percent [$\Delta\%$]) in waist circumference (-5.2, -3.8%) and in tricipital (-13.3, -13.6%), supra-iliac (-19.4, -13.6%), and abdominal skinfold (-18.2, -15.6%) in both the HIT-IR and HIT-CON groups (Table 1).

Cardiovascular measurements

At baseline, there were no significant ($P \leq 0.05$) differences between groups for diastolic or systolic blood pressure (Table 1). After intervention, the HIT-CON showed significant pre-post changes in systolic (-2.3%) (Table 2). In both groups, there were no significant ($P > 0.05$) changes for diastolic blood pressure (Table 2).

Metabolic measurements

At baseline, there were significant ($P \leq 0.05$) differences between groups for fasting glucose, fasting insulin, and HOMA-IR (Table 2). After intervention, in the HIT-CON group, there were no pre-post changes in fasting glucose, fasting insulin, HOMA-IR in HIT-CON group (Table 2). There were significant ($P \leq 0.05$) pre-post changes (presented as delta percent ($\Delta\%$)) in fasting glucose (-8.8%), fasting insulin (-26.5%), and HOMA-IR (-32.1%) in the HIT-IR group (Table 2). There were large ES values for fasting glucose -1.65 (-2.07, -1.22) and HOMA-IR -1.23 (-1.60, -0.85) in the HIT-IR group (Table 2).

Performance measurements

At baseline, there were no significant ($P \leq 0.05$) differences between groups for $1RM_{LE}$ and $1RM_{UR}$ (Table 2). After intervention, there were significant ($P \leq 0.05$) pre-post changes in $1RM_{LE}$ in the HIT-IR (+12.9) and in HIT-CON (+14.7%) groups (Table

2), whereas $1RM_{UR}$ remained unchanged in both groups. There were large ES values for $1RM_{LE}$ 1.25 (1.04, 1.45) in the HIT-CON group (Table 2).

Differences in NR prevalence between the HIT-IR vs. HIT-CON groups with respect to glucose control variables

There were significant differences between the HIT-IR vs. HIT-CON groups in NR prevalence with regard to improve fasting glucose (25.0% vs. 95.0%, $P<0.0001$) and fasting insulin (25.0 vs. 60.0%, $P=0.025$). There were no significant differences between the HIT-IR vs. HIT-CON groups in NR prevalence with regard to a decrease in HOMA-IR (25.0% vs. 45.0%, $P=0.185$) (Figure 2).

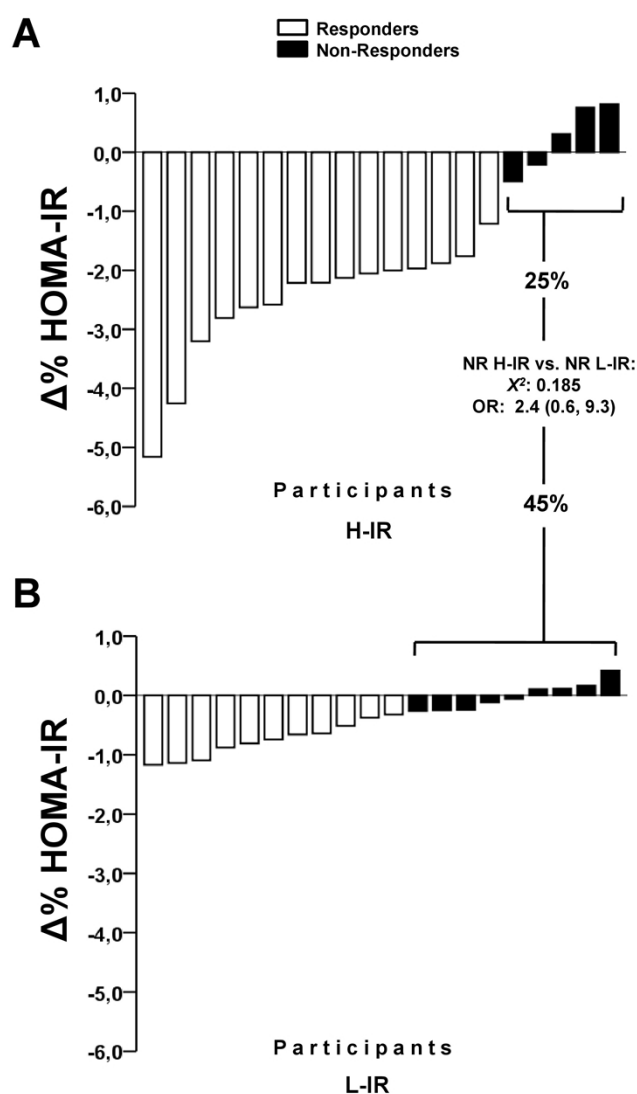


Figure 2. Differences in the prevalence of non-responders to decrease HOMA-IR after high-intensity interval training in a higher insulin resistant (H-IR, $N = 20$), and lower insulin resistant group (L-IR, $N = 20$) adult woman. OR: odds ratios for suffering a non-response.

Differences in NR prevalence between the HIT-IR vs. HIT-CON groups with respect to other body composition, cardiovascular, and performance variables

There were no significant differences between the HIT-IR vs. HIT-CON groups in NR prevalence with regard to improvement of the body composition (i.e., body mass, BMI, waist circumference, tricipital, supra-iliac, and abdominal skinfolds), muscle

performance (i.e., $1RM_{LE}$ and $1RM_{UR}$), as well as cardiovascular parameters (i.e., systolic/diastolic blood pressure) (Table 3). The Odds Ratios (OR) of the NR prevalence detected a high risk (> 2 fold) to improve waist circumference (OR: 2.1), diastolic blood pressure (OR: 2.1), fasting glucose (OR: 4.0) and $1RM_{UR}$ (OR: 2.1) (Table 3).

Table 3. Prevalence of non-responders (NR) on body composition, cardiovascular, metabolic, and performance parameters after 10-weeks high-intensity interval training in a higher insulin resistance (H-IR), and lower (L-IR) group of IR adult women.

	Response	H-IR	L-IR	OR (95% CI)	P value NRs H-IR vs. NR L-IR
N =		20	20		
body composition					
Body mass (% / n =)	NR	20.0 (4)	10.0 (2)	0.4 (0.7, 2.7)	P=0.376
	R	80.0 (16)	90 (18)		
Body mass index (% / n =)	NR	25.0 (5)	10.0 (2)	0.3 (0.5, 1.9)	P=0.212
	R	75.0 (15)	90.0 (18)		
Waist circumference (% / n =)	NR	5.0 (1)	10.0 (2)	2.1* (0.1, 3.2)	P=0.548
	R	95.0 (19)	90.0 (18)		
Tricipital skinfold (% / n =)	NR	5.0 (1)	5.0 (1)	1.0 (0.5, 0.9)	P=0.987
	R	95.0 (19)	95.0 (19)		
Supra-iliac skinfold (% / n =)	NR	30.0 (6)	30.0 (6)	1.0 (0.2, 3.8)	P=0.944
	R	70.0 (14)	70.0 (14)		
Abdominal skinfold (% / n =)	NR	10.0 (2)	5.0 (1)	0.4 (0.3, 5.6)	P=0.543
	R	90.0 (18)	95.0 (19)		
Cardiovascular					
Systolic blood pressure(% / n =)	NR	55.0 (11)	70.0 (14)	1.9 (0.5, 7.0)	P=0.327
	R	45.0 (9)	30.0 (6)		
Diastolic blood pressure (% / n =)	NR	90.0 (18)	100 (20)	2.1* (1.5, 2.9)	P=0.147
	R	10.0 (2)	0 (0)		
Metabolic/plasmatic					
Fasting glucose (% / n =)	NR	25.0 (5)	95.0 (19)	4.0* (6.2, 14.4)	P<0.0001
	R	75.0 (15)	5.0 (1)		
Fasting insulin (% / n =)	NR	25.0 (5)	60.0 (12)	4.5 (1.1, 4.3)	P=0.025
	R	75.0 (15)	40.0 (8)		
Strength performance					
1RM _{LE} (% / n =)	NR	10.0 (2)	0 (0)	0.4 (0.3, 0.6)	P=0.147
	R	90.0 (18)	100 (20)		
1RM _{UR} (% / n =)	NR	20.0 (4)	35.0 (7)	2.1* (0.5, 9.0)	P=0.288
	R	80.0 (16)	65.0 (13)		

Data are percentage, % / n = number of cases. 1RM_{LE}: one-maximum repetition of leg extension; 1RM_{UR}: one-maximum repetition of upper row. * Denotes a high risk (> 2 fold) for suffering a non-response.

Discussion

The present study was designed to assess the effects and NR prevalence (as indicated by glucose control variables) after 10-weeks of HIT in IR and metabolic-healthy adult women. The major findings of this study indicate that *i)* HIT promotes significantly more benefits in training-induced changes in fasting glucose, fasting insulin and HOMA-IR in IR adult women than in metabolic-healthy control adult women, *ii)* NR prevalence between the HIT-IR vs. HIT-CON groups was significantly different with regard to improve fasting glucose and fasting insulin, but not HOMA-IR marker, and *iii)* both HIT-IR and HIT-CON groups induced similar positive training-induced changes as well as similar NR prevalence with regard to body composition (body mass, BMI), cardiovascular (systolic/diastolic blood pressure), and performance measures ($1RM_{LE}$, $1RM_{UR}$).

Several environmental factors in NR prevalence have been reported after training interventions. For example, a recent report assessed the effects of resistance training at different frequencies/week (3 and 2 days/week, testing the frequency factor) in older NR subjects for 12- and 24-weeks. Major differences between both training regimens were found in body mass, which decreased ~4.5% at 12-weeks and 23% at 24-weeks. Interestingly, other results included increases in type I (+34.5 vs. +29.4%) and type II muscle fibers (+22.7 vs. +21.1%), as well as increasing strength in leg extension exercise (+0.9 vs. +1.17%) at 12- and 24-weeks, which were relatively similar results independent of the training frequency. These results indicated that the frequency of training was not necessarily related to NR prevalence for some variables (Churchward-Venne et al., 2015).

There is limited evidence about inter-individual variability in exercise training with regard to the NR prevalence in subjects with low glucose control, and there are several methodological differences in comparing the NR prevalence observed in these previous studies (Boulé et al., 2005; Gremeaux et al., 2012; Higgins et al., 2015; Moker et al., 2014; Winett et al., 2014; Yates et al., 2013). For example, for glucose control variables, several authors have observed that after 3-months of strength training (2 days/week, 2 strength exercises, at maximal effort), the NR prevalence for improvements of the oral glucose tolerance test (OGTT) in pre-diabetic patients was 44%. In the present study, we found a NR prevalence of 15% and 25% in the HIT-IR and CON groups, respectively, for decreased fasting glucose, with no significant difference between the groups (Table 3) (Winett et al., 2014). Regarding HOMA-IR, the HERITAGE study (Boulé et al., 2005) showed that after 20-weeks of endurance training (30-50 min/session, 55-75% VO_{2max} , 20-weeks), 42% of subjects were NR for an increase in HOMA-IR. We found similar results regarding a decrease in HOMA-

IR, with a NR prevalence of 15% and 20% for the HIT-IR and HIT-CON groups, respectively (Figure 2).

Therefore, considering our 10-weeks of HIT-based exercise vs. the 20-weeks of endurance exercise in the abovementioned study (Boulé et al., 2005), the ‘volume’ factor may not necessarily increase the NR prevalence in glucose control variables such as HOMA-IR. In a different study (Yates et al., 2013), there was a reported 3% NR prevalence for decreased fasting glucose after 12-months of exercise intervention. Similarly, when T2DM subjects were tested after 9-months of endurance, strength or concurrent training, another study (N. A. Stephens et al., 2015) showed that 21% of subjects were NR for decreased HbA1c and other body composition and protein markers.

Understanding the NR prevalence after exercise modes such as HIT can be useful for designing more efficient exercise interventions; in this case, populations with altered baseline, such as the HIT-IR group for the variables fasting glucose and HOMA-IR, are less likely to be NR cases after 10-weeks of HIT. This altered baseline, which we termed previously ‘metabolic-healthy status’, is a potential factor for predicting responses in future long-term studies. Collectively, and in combination with previous reports (Hecksteden, Grütters, & Meyer, 2013b), these findings indicate that the ‘magnitude’ of changes in response to an acute exercise session can be a potential factor for predicting responses to chronic exercise interventions. In this study, the magnitude of plasma changes after volitional exercise showed a high correlation between those subjects who had decreased fasting insulin after chronic exercise training (walking/running at 60% $\text{VO}_{2\text{peak}}$, for 4-weeks).

Another study (Moker et al., 2014) exploring one of the other co-variables, blood pressure, showed that after 5-months of endurance (65-80% $\text{VO}_{2\text{peak}}$, walking/jogging), strength (8-12 repetitions per set, 8 exercises, 70-85% of 1RM), or concurrent training, approximately ~60% of subjects were NR for a decrease in systolic and diastolic blood pressure. In our study, we found NR prevalence of 20% and 15% for decreased systolic blood pressure in the HIT-IR and HIT-CON groups, respectively, as well as more pronounced NR prevalence of 30% and 45% for decreased diastolic blood pressure in the HIT-IR and HIT-CON groups, respectively (Table 3). Because none of the intervention groups were diagnosed with hypertension, we hypothesized that genetic factors together with time of intervention, mode of training, and the non-hypertensive baseline profile may be responsible for these results. However, these results were more positive after 10-weeks of HIT than the 60% NR prevalence observed in the aforementioned study with 5-months of intervention. Thus, the volume

of training does not play an apparent role in NR prevalence for decreases in systolic or diastolic blood pressure.

Evidence has shown the benefit in decreasing systolic blood pressure after HIT interventions (Emmanuel Gomes Ciolac, 2012); however, in this non-hypertensive cohort, we did not observe significant training-induced changes in systolic or diastolic blood pressure (Table 2). In other studies, there was a ~60% NR prevalence for decreased systolic or diastolic blood pressure after 6-weeks (Higgins et al., 2015) or 6-months (Moker et al., 2014) of HIT. Interestingly, a study that explored the magnitude of the changes in blood pressure after an acute exercise session reported that this factor can be used as a predictive factor for decreasing blood pressure after long-term exercise training (Hecksteden, Grütters, & Meyer, 2013a).

In this study, we found significant training-induced changes in the $1RM_{LE}$ test in the HIT-IR (+12.9%) and HIIT-CON (+14.7%) groups (Table 2). Similarly, we found a 10% NR prevalence for an increase in $1RM_{LE}$ in the HIT-IR and no cases (0%) of NR in the HIT-CON group (Table 3). However, in previous studies, resistant training (10-15 repetitions, 4 sets of leg extension, 60-80% 1RM) resulted in a minimum of ~1% NR prevalence for an increase in $1RM_{LE}$ after 12- and 24-weeks of resistant training (Churchward-Venne et al., 2015). Additionally, despite the fact that our HIT mode of training is very different methodologically than what was reported in previous studies, the HIT protocol was able to increase the strength of the lower limbs. These findings are consistent a previous HIT-based study (90 s, 6 bouts, 6 weeks), in which HIT improved several parameters of power cycling in the lower limbs in adult men (Ziemann et al., 2011).

We observed different ranges of NR prevalence for other body composition (5-30%), blood pressure (55-100%), plasma (25-95%), and performance (0-35%) variables. These results are consistent with literature reports for blood pressure (59-60%) (Moker et al., 2014), plasma (7-44%) (Boulé et al., 2005; Osler et al., 2015; N. A. Stephens et al., 2015; Winett et al., 2014; Yates et al., 2013), and performance (1%) variables (Churchward-Venne et al., 2015).

Strengths and limitations

Finally, our study has some important limitations. Our sample size was limited, but it is similar to the sample sizes used in other exercise training studies (~10 to 20 subjects). Additionally, we lacked a true no-exercise control group, and we did not control the physical activity patterns and diet after training, although subjects were reminded each week to maintain their baseline patterns. The strengths of this study

were that we included both effects on and NR prevalence of changes in body composition, cardiovascular, plasma and performance variables, and we included the statistical ES for each variable studied.

Conclusion

In conclusion, independent of the IR vs. metabolic-healthy control status, non-response prevalence to improve HOMA-IR glucose control parameter, as well as body composition, cardiovascular, and performance measures were similar after 10-weeks of HIT in sedentary adult women with IR. This research demonstrates the efficacy of exercise training, as well as the similar NR prevalence to provide a cardioprotective effect against progression from IR to T2DM in a sedentary adult female population independently of the health status.

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Chapter 4

Effects of 6-weeks high-intensity interval training in schoolchildren with insulin resistance: influence of biological maturation on metabolic, body composition, cardiovascular and performance non-responses

* **Cristian Alvarez**, Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez and Mikel Izquierdo. Effects of 6-Weeks High-Intensity Interval Training in Schoolchildren with Insulin Resistance: Influence of Biological Maturation on Metabolic, Body Composition, Cardiovascular and Performance Non-responses. *Frontiers in physiology*; 2017, (8):444.

Effects of 6-weeks high-intensity interval training in schoolchildren with insulin resistance: influence of biological maturation on metabolic, body composition, cardiovascular and performance non-responses

Abstract

Background/aims: Previous studies have observed significant heterogeneity in the magnitude of change in measures of metabolic response to exercise training. The aim of this study was to compare the effects and prevalence of NR to improve the IR level, as well as to other body composition, cardiovascular, and performance co-variables, between early (EM) and normal maturation (NM) in IR schoolchildren after 6-weeks of HIT. **Methods:** Sedentary children (age 11.4 ± 1.7 years) were randomized to either HIT-EM group ($N = 12$) or HIT-NM group ($N = 17$). Fasting glucose (FGL), fasting insulin (FINS) and HOMA-IR were assessed as the main outcomes. **Results:** There were no significant differences between groups in the prevalence of NR based on FGL, FINS, and HOMA-IR. There were significant differences in NR prevalence to decrease co-variables body mass (HIT-EM 66.6% vs. HIT-NM 35.2%) and SBP (HIT-EM 41.6% vs. HIT-NM 70.5%). A high risk [based on odds ratios (OR)] of NRs cases was detected for FGL, OR = 3.2 (0.2 to 5.6), and HOMA-IR, OR = 3.2 (0.2 to 6.0). **Conclusions:** Although there were no differences in the prevalence of NR to metabolic variables between groups of IR schoolchildren of different maturation starting, other differences were found to body mass and SBP, suggesting that body composition and cardiovascular parameters can be playing a role in the NR prevalence after HIT. These results were displayed with several metabolic, body composition, blood pressure, and performance improvements independent of an early/normal maturation or the prevalence of NR.

Keywords: inter-individual variability, biological maturation, diabetes, performance, high-intensity interval training

Introduction

The benefits of exercise on health and performance are mainly expressed in terms of the 'mean', but there is wide inter-individual variability in response to exercise training (IVRET) that has not been fully clarified in adults (Cristian Alvarez, Ramírez-Campillo, Ramírez-Vélez, & Izquierdo, 2017; Claude Bouchard et al., 2012; Montero & Lundby, 2017; Sisson et al., 2009) and not explored in children. IVRET means that under the same stimulus, some subjects may achieve positive benefits after training (i.e., responders-R), while others exhibit a worsened or unchanged response and are thus termed non-responders (NR) (Bonafiglia et al., 2016; Sisson et al., 2009). For example, although the mean of a group may indicate decreased fasting glucose after training, individuals in this group could show no changes or a worsened response and would thus be considered as NR in terms of fasting glucose (Alvarez et al., 2017). Studies using endurance and high-intensity interval training (HIT) in adults have described the occurrence of IVRET in performance variables such as maximum aerobic power (Prud'homme et al., 1984), maximum oxygen consumption (VO_2max) (C. Bouchard & Rankinen, 2001b), and heart rate (Astorino & Schubert, 2014). More recently, others authors have described that under the same HIT or resistance training (RT) regimens or under different health status conditions, there are similar and different prevalence of NR (i.e., percentage of NR cases) defined by improved body composition, cardiovascular, metabolic and performance variables in adults (C. Álvarez, Ramírez-Campillo, Ramírez-Vélez, & Izquierdo, 2017; Alvarez et al., 2017)

Previous experimental trials has shown high intensity protocols consisting of 8–10 1 min bouts of high-intensity exercise to be effective at improving both insulin and glucose parameters in adolescents (Bond et al., 2015; Cockcroft et al., 2017; Cockcroft et al., 2015). However, despite of IR increases with age, racial health disparities and pubertal status (Ball et al., 2006), some authors have shown in girls and boys from 9 to 16 years an interesting relationship between physical activity and decreases in both insulin and HOMA-IR changes throughout development (Metcalf et al., 2015).

On the other hand, age/pubertal status has been reported to be highly associated with more overweight/obesity (Wang, 2002). Analyses from HELENA Study, showed high discrepancies between chronological and biological age in cardiorespiratory and strength performance (Ortega et al., 2008). Similarly, clear differences between those who were middle-pre pubertal vs. late-pubertal regarding the level of metabolic substrate used during exercise have been observed (B. Stephens, Cole, & Mahon, 2006).

It is unclear whether the metabolic benefits of exercise training are limited to those IR children with earlier (EM) and normal (NM) initiation of biological maturation. To the best of the author's knowledge, the role of early maturation and the prevalence of NR after a short-term HIT intervention in children with IR is limited. Thus, despite that maturity has not showed a clear role on performance (Marta, Marinho, Izquierdo, & Marques, 2014) in children, and considering that there is a lack of studies in glucose control parameters including the IVRET topic, it could, therefore, be suggest that one responsible of the chronic effects of exercise on glucose and insulin are dependent on age/pubertal status (Chu, Riddell, Schneiderman, McCrindle, & Hamilton, 2014), with adolescents having a greater scope for improvements compared to younger children.

Thus, our objective was to compare the effects and prevalence of NR to improve the IR level (by HOMA-IR), as well as to other body composition, cardiovascular, and performance co-variables, by early (EM) or normal maturation (NM) in IR schoolchildren after 6-weeks of HIT. We hypothesized that regardless of biological maturation, there would be no difference in the prevalence of NR according to level of glycaemic control as defined by fasting glucose, fasting insulin and HOMA-IR in IR children after a short HIT regimen.

Material and methods

Participants and study design

Initially, 150 schoolchildren (aged between 8 and 13 years), both boys and girls, with no background of regular HIT volunteered to participate in this study. The eligibility criteria included the following: a) age between 8 and 13 years (to include children with the capacity to follow the exercise instructions; b) address in an urban area; c) diagnosis of IR in the screening applied at school (≤ 3 months) according to one of three glucose control markers: HOMA-IR ≥ 2.6 and following cut-off point of a similar Chilean cohort of children (R. Burrows et al., 2015), fasting insulin levels $> 15 \mu\text{U/dL}$ (Reaven et al., 1993), or fasting glucose > 100 and $< 126 \text{ mg/dL}$ (WHO, 1999); d) physical inactivity ($\leq 60 \text{ min/day}$ of moderate physical activity) (Gary O'Donovan et al., 2010; G. O'Donovan et al., 2010; WHO, 2010); and e) participation in the normal physical education class each week. The exclusion criteria included participants with: a) potential medical problems or a history of a familial metabolic disease such as T2DM in parents, b) ischemic disease, c) arrhythmia, d) asthma, e) chronic obstructive pulmonary disease, or f) utilization of drugs that modulate metabolic and respiratory control.

This study was designed to address the question of how a HIT school-based program affects the NR prevalence as defined by improved metabolic glucose control [fasting glucose, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR)], as well as other body composition, cardiovascular, and performance co-variables independent of different biological maturation stages in schoolchildren with IR. To accomplish this, we screened subjects at school to detect IR subjects, and after a short HIT program, we compared the effects of 6-weeks of HIT in two groups of children with different start times of biological sexual maturation: EM and NM.

In the 1st stage (enrolment stage), one-hundred and six subjects were not included for multiple reasons among subjects with both early and normal maturation: a) age < 8 years or > 13 years, b) direct familial history of T2DM, c) diagnosed asthma, d) participation in regular physical activity, e) address in a rural areas, and f) no diagnosed criterion of IR. Subsequently, forty-four subjects including those with EM and normal maturation (NM) were identified with IR at screening, and were allocated into 2 groups: a HIT early maturation group (HIT-EM, $N = 25$) and a HIT normal maturation group (HIT-NM, $N = 21$). Thus, the final sample analysed was as follows: HIT-EM, age $11.0 \pm 1.0 \text{ y}$, BMI 26.2 ± 5.6 , $N = 12$ and HIT-NM, age $12.0 \pm 1.0 \text{ y}$, BMI 27.0 ± 4.7 , $N = 17$. Subjects with $< 70\%$ training attendance were excluded from all statistical

analyses. The final exercise compliance was of 81.4 ± 3 , and $83.1 \pm 6\%$ to each HIT-EM and HIT-NM group, respectively.

Participants (and their parents/guardians) were informed of the experimental procedures at a meeting with the research team and were informed about the possible risks and benefits associated with participation in the study; signed and informed consent was also obtained at this meeting and before any of the assessments were performed. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board for studies with human subjects of the local Ethics Committee of the University of Los Lagos (Comité de Revisión Científica y Ética Institucional del Departamento de Ciencias de la Actividad Física de la Universidad de Los Lagos). The size of the sample was computed according to the delta changes observed in the delta changes of fasting glucose ($\Delta\text{FGL} = 2.3$; $\text{SD} = 1.7$ mg/dL) in a group intervened with a similar intervention (C. Álvarez, Ramírez, Flores, Zúñiga, & Celis-Morales, 2012). A statistical power analysis revealed that a total of 12 participants per group would yield a power of 80% at a $P < 0.05$ alpha level. The procedures were established according to the “CONSORT” statement, which can be found at <http://www.consort-statement.org>. Further details regarding the sample are presented in (Figure 1).

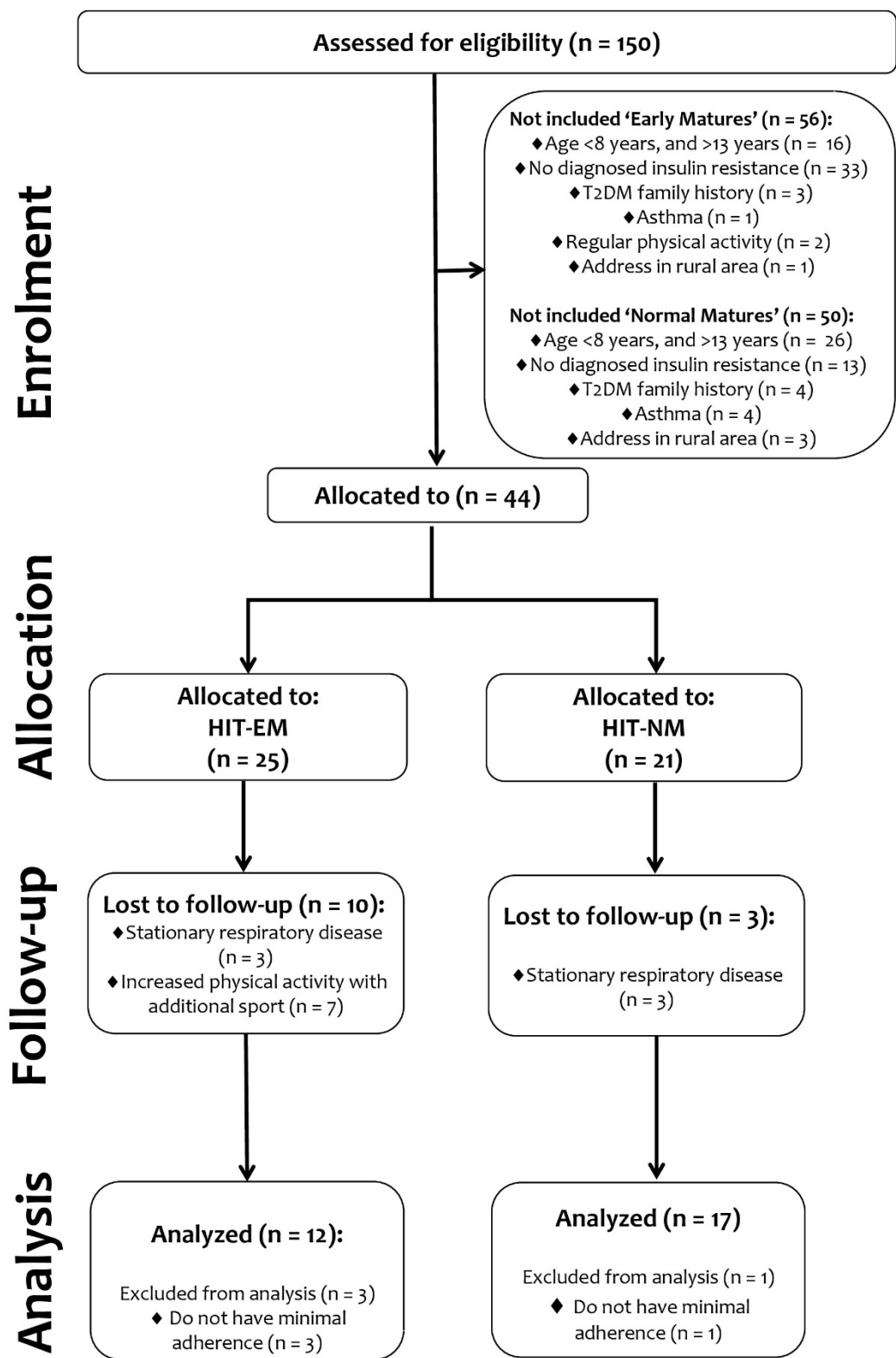


Figure 1. Study design.

During the 1st and 2nd week, participants were familiarized with the test procedures in 6 sessions (2 theoretical classes about the exercise procedures and 4 sessions to practice HIT) before the initial assessment to understand the machines and weights as well as the protocols of the test. In the 3rd week before the performance measurements, subjects did not engage in any additional exercise training other than their regular physical education class (2 classes of 90 min), as this would disrupt the HIT scheme. In week 4, the measurements were conducted in the following order: plasma samples were drawn in the morning and body composition assessments were

performed in the afternoon (Monday). After 48 h, blood pressure measurements were taken, and tests of strength performance occurred in the morning and endurance performance in the afternoon (Wednesday and Friday). The measurements were completed in 5 days following the same order at the same time by the same professionals. In the 5th week, to reduce the potential effect of cumulative fatigue on dependent variables before and after the intervention, subjects had 7 days of rest between the last training and the first measurement session. Participants were instructed to wear similar athletic clothes during all testing sessions, as well do not drink water with ergogenic effects (tea, coffee, or sugar meals) before and after training for hydration. Before the screening at school and allocation, 5-weeks were necessary to complete all the assessments, being the last 2-weeks used in the familiarization process, and the intervention was thus started in week 6. Before the intervention, there were significant baseline differences between groups in the dependent variables of genital maturation, height, and body mass. Other than these variables, there were no significant differences between groups in baseline characteristics (Table 1 and Table 2).

Table 1. Biological maturation characteristics and body composition pre-post changes of the subjects.

Variable	Test	HIT-EM (N = 12)	Effect size	HIT-NM (N = 17)	Effect size	Pvalue HIT EM vs. HIT-NM Baseline	Pvalue HIT EM vs. HIT-NM Pre-Post
Gender (♀ / ♂)		7 / 4		9 / 8			
Age (y)	Pre	11.0 ± 1.0		12.0 ± 1.0		P=0.067	
Genital maturation	Pre	1.9 ± 1.0		2.9 ± 0.9		P<0.01	
Pubic hair maturation	Pre	3.0 ± 1.0		3.0 ± 1.0		P=0.229	
Height (cm)	Pre	145.0 ± 0.11		153.0 ± 0.06		P<0.01	P<0.01
	Post	146.3 ± 0.06		154.6 ± 0.09			
Boby composition							
Body mass index (m·kg ⁻²)	Pre	26.2 ± 5.6	0.02 (-0.07, 0.10)	27.1 ± 4.7	-0.08 (-0.14, -0.02)	P=0.633	P=0.023
	Post	26.3 ± 5.4		26.7 ± 4.2			
	Pvalue	P=0.322		P=0.065			
	Δ%	0.3		-1.4			
Waist circumference (cm)	Pre	86.8 ± 14.0	-0.01 (-0.31, 0.04)	88.0 ± 9.8	-0.22 (-0.35, -0.10) ^{\$}	P=0.801	P=0.345
	Post	84.6 ± 13.2		85.7 ± 9.1			
	Pvalue	P=0.144		P=0.139			
	Δ%	-2.5		-2.6			
Supra-iliac skinfold (mm)	Pre	42.5 ± 10.8	-0.44 (-0.60, -0.29) ^{\$}	41.1 ± 6.7	-1.24 (-1.55, -0.92) [‡]	P=0.661	P=0.056
	Post	35.7 ± 9.0		33.3 ± 5.8			
	Pvalue	P<0.01		P=0.01			
	Δ%	-16.0		-18.9			

Note. Data presented as mean and ±SD. Delta changes (Δ%) is presented in percentage. Groups are described as HIT-EM = high intensity interval training earlier matures; HIT-NM = high intensity interval training normal matures. Variables are described as ♀ = girls; ♂ = boys. Bold values indicate significant differences at level P≤0.05. ^{\$} Small standardized effect at level P ≤ 0.05. [‡] Large standardized effect at level P≤0.05.

Table 2. Characteristics and pre-post changes of the subjects at level of blood pressure, metabolic, and performance variables.

Variable	Test	HIT-EM (N = 12)	Effect size	HIT-NM (N = 17)	Effect size	Pvalue HIT EM vs. HIT-NM Baseline	Pvalue HIT EM vs. HIT-NM Pre-Post
Strength performance							
1RM _{LE} (kg)	Pre	14 ± 6	0.67 (0.22, 1.12) [§]	19 ± 6	0.92 (0.36, 1.48) [§]	P=0.089	P=0.678
	Post	20 ± 8		27 ± 6			
	Pvalue	P=0.060		P<0.001			
	Δ%	+42.8		+42.1			
1RM _{UR} (kg)	Pre	6 ± 2	0.89 (0.27, 1.51) [§]	8 ± 3	0.58 (0.11, 1.06) [§]	P=0.114	P=0.334
	Post	8 ± 3		10 ± 4			
	Pvalue	P=0.093		P<0.001			
	Δ%	+33.3		+25.0			

Note. Data presented as mean and ±SD. Delta changes (Δ%) is presented in percentage. Groups are described as HIT-EM = high intensity interval training earlier matures; HIT-NM = high intensity interval training normal matures. Variables are described as 1RM_{LE} = 1 maximum repetition leg-extension; 1RM_{UR} = 1 maximum repetition upper row. Bold values denotes significant pre-post changes intra group. [§] Small standardized effect at level P≤0.05. [§] Moderate standardized effect at level P≤0.05.

Classification of responders (R) and non-responders (NR)

Following previous criteria applied in exercise interventions (Bonafiglia et al., 2016), the IVRET of the subjects was categorized into responders R and NR using the typical error method (TE). The TE was calculated for the main outcomes (fasting glucose, fasting insulin and HOMA-IR), as well as for the other body composition, cardiovascular, and performance co-variables, as described previously (Will G. Hopkins, 2000), using the following equation:

$$TE = SD_{diff} / \sqrt{2}$$

Where SD_{diff} is the variance (standard deviation) in the difference in scores observed between the 2 repeats of each test. The NR to decrease fasting glucose, fasting insulin, and HOMA-IR, as well as in all the co-variables, were defined as those individuals who failed to demonstrate an increase or decrease (in favour of beneficial changes) greater than 2 times the TE away from zero. A change 2 times greater than the TE indicated a high probability (i.e., 12 to 1 Odds) that this response x was a true physiological adaptation beyond what might be expected x from technical and/or biological variability (Will G. Hopkins, 2000).

Classification of start of biological maturation

Subjects' biological maturation was classified using a self-reported personal questionnaire that assessed Tanner stages (pubic hair stages for both sexes, breast stage for girls, and genitalia stage for boys) that has been used previously (Matsudo & Matsudo, 1994). The subjects were briefly informed about the questionnaire by a specialist. A male subject was classified as in the 'early maturation' group if the development of his genitalia was scored as stage 2 and his chronological age was less than the average age of the sample with a genitalia stage 2; we previously calculated the average age of individuals in each Tanner stage (1 to 5) in boys and girls (Wang, 2002). This classification allowed us to identify to some chronological age when a child was in the 'mean biological maturation' or was younger than this value (i.e., early maturation) according to each Tanner stage.

Metabolic measurements

Subjects arrived with their parents to the Riñihue's clinic between 08.00 and 10.00 in the morning after 10 h of overnight fasting, and blood samples (3.5 mL) were collected in tubes with specific anticoagulant gel to collect glucose and insulin. Samples were immediately placed on ice and centrifuged at 4,000 rpm (1700 x g) for 5 minutes

at 4 °C. Plasma samples were immediately transferred to pre-chilled microtubes and stored at -20 °C for later analysis. Plasma glucose was analysed by enzymatic methods using standard kits (Wiener Lab Inc., Rosario, Argentina) with an automatic analyser (Metrolab 2300 Plus™, Metrolab Biomed Inc., Buenos Aires, Argentina). Fasting insulin was measured by RIA (DPC, Los Angeles, CA, USA). The HOMA-IR index was calculated using the Matthews equation (Matthews et al., 1985): $\text{insulin resistance (IR)} = [\text{glucose (mg/dL)} \times \text{insulin (}\mu\text{U/dL)}] / 405$. The same blood sampling and preparation procedures were performed at the end of the 6-weeks follow-up 48 h after the last exercise session to avoid the possible acute effects of exercise.

Body composition measurements

Body composition measurements were taken after plasma blood sampling, 3 days before the performance measurements. Body mass (in kilograms) was assessed using an electrical bio-impedance scale with 0.1 kg accuracy (Omron HBF-INT™, Omron Healthcare Inc., Lake Forest, IL, USA), similar to other studies (Corte de Araujo et al., 2012). Standing height (in inches) was assessed with a professional stadiometer (Health o Meter™ Professional, Sunbeam Products Inc., Chicago, IL, USA) to an accuracy of 0.1 cm, and BMI was calculated (kg/m). Waist circumference was assessed with an inextensible measuring tape with 0.1 cm accuracy (Hoechstmass™, Sulzbach, Germany). Additionally, 3 skinfold measurements of subcutaneous adipose tissue (tricipital, suprailiac, and abdominal skinfold) were assessed using a Langue™ skinfold caliper (Beta Technology Inc., Santa Cruz, California, USA) according to standard protocols (Marfell-Jones, 2006).

Strength performance measurements

Muscle performance tests were conducted as previously reported (Faigenbaum et al., 1996). Two one-repetition maximum (1RM) strength tests were performed: 1RM leg extension (1RM_{LE}) using an exercise machine (OXFORD™, model EE4002, Santiago, Chile) and the 1RM of upper row (1RM_{UR}) test using weights and metal bars. The highest load of three attempts per exercise was recorded. The test procedure was repeated at the same time and in the same order as the post-intervention measurement by the same evaluator, who was blinded to subject's group assignment.

High-intensity interval training program

A total of 18 sessions (3 times per week) were conducted in the HIT program. Cycle ergometers adapted for children (OXFORD™, model BE2601, OXOFORD Inc, Santiago, Chile) were used. Each participant performed a range of 8 to 12 cycling

intervals (weeks 1-2; 8, weeks 3-4; 10, weeks 5-6; 12 intervals) during the intervention period. The duration of each cycling interval increased progressively each week and ranged between 40 and 60 s (40 s weeks 1-2; 50 s weeks 3-5; 60 s week 6), with 120 s of passive rest (on the bicycle without movement) between each work interval. Cycle revolutions were determined at a range of 50-70 revolutions per min (rpm) and a speed between 20 and 40 km/h during each work interval.

The modified Borg scale (RPE) was applied to assess subjective effort as a marker of intensity to guide the training, specifically to maintain a score between 8 and 10 RPE points during each cycling interval (Emmanuel Gomes Ciolac et al., 2015), and the cycloergometer load was adjusted every ~2 weeks to maintain this subjective intensity during cycling. This subjective intensity corresponded to a range of 70 to 100% of maximum heart rate according to the Karvonen formula (Karvonen, 1988). A professional physiologist provided the respective instructions to start each work interval during the sessions. Each training session was performed in the afternoon from 4 to 6 pm throughout the 6-weeks period, and was closely monitored by exercise physiologists (Behm, Faigenbaum, Falk, & Klentrou, 2008). All subjects had good exercise tolerance, and none of the participants reported an injury. The exercise compliance was $80.0 \pm 1\%$ in the HIT-EM and $94.4 \pm 3\%$ in the HIT-NM during the follow-up. Characteristics of the training sessions are presented in (Table 3).

Table 3. Characteristics of the HIT training.

Variable	Week	Week	Week	Week	Week	Week
	1	2	3	4	5	6
Duration of interval of work (sec)	40	40	50	50	60	60
Duration of interval of rest (sec)	120	120	120	120	120	120
Number of intervals of work (Nº)	8	8	10	10	12	12
Number of intervals of rest (Nº)	9	9	11	11	13	13
Qualitative intensity in Borg scale 1-10 (pts)	8-10	8-10	8-10	8-10	8-10	8-10
Quantitative intensity by heart rate (%)	70-100	70-100	70-100	70-100	70-100	70-100
Cadence (rpm)	50-70	50-70	50-70	50-70	50-70	50-70
Velocity (km/h)	20-40	20-40	20-40	20-40	20-40	20-40
Volume of work / session (min)	5.3	5.3	8.3	8.3	14	14
Volume of work / week (min)	15.9	15.9	24.9	24.9	42	42
Volume of rest / session (min)	18	18	22	22	26	26
Volume of rest / week (min)	54	54	66	66	78	78
Total time investment / session (min)	23.3	23.3	30.3	30.3	40.0	40.0
Total time investment / week (min)	69.9	69.9	90.9	90.9	120.0	120.0
Total time investment / 6-weeks (h)	-	-	-	-	-	4.68

Note: sec = seconds; Nº = numbers; pts = points; % = percentage; rpm: revolutions per minute; km/h = kilometres per hour; min = minutes; h = hours.

Statistical analysis

Data are presented as the mean \pm standard deviation (SD). Assumptions of normality and homoscedasticity for all data were checked using the Shapiro-Wilk and Levene tests, respectively. Wilcoxon test was used for non-parametric data (waist circumference, systolic BP, and $1RM_{UR}$). One-way ANOVA was conducted to test for differences between baseline groups. ANCOVA was performed to assess differences in baseline body mass using WC and the 3 skinfold measurements as co-variables. A repeated-measures ANOVA with 2 factors (groups x time) was used to determine the differences in all dependent variables between the pre- and post 6-weeks tests using each group x time interaction. After the intervention, delta values (Δ) in percentages (%) were calculated between pre-and post-intervention assessments of fasting glucose, fasting insulin, and HOMA-IR. Subjects were categorized as R or NR using the TE method for each dependent variable according to the previously described criteria of 2 TE (Bonafiglia et al., 2016). Bonferroni *post hoc* test was applied to establish the differences between groups. Additionally, Cohen's test was used to detect the Cohen effect size (d) test, with threshold values of 0.20, 0.60, 1.2, and 2.0 for small, moderate, large, and very large effects, respectively (William G. Hopkins et al., 2009). To test for differences between R and NR by HIT-EM x HIT-NM groups, Chi-Square test (X^2) was used for categorical variables. The odds ratios (OR) of being a non-responder were calculated for the differences in dichotomous NR variables between groups. All statistical analyses were performed with SPSS statistical software version 18 (SPSSTM Inc., Chicago, Illinois, USA). The alpha level was fixed at $P \leq 0.05$ to indicate statistical significance.

Results

Baseline

Before training, there were significant ($P<0.05$) differences between groups in genital maturation, height, and body mass (Table 1).

Training-induced changes

After training, in the HIT-EM group, no significant changes were observed in body mass (Figure 2), BMI and WC (Table 1), DBP (Figure 3D), FGL and $1RM_{LE}$ (Figure 4A and Table 2). In the HIT-NM group, no significant changes were observed in body mass (Figure 2A), BMI and WC (Table 2), systolic/diastolic BP (Figure 2A and Figure 2D) and FGL (Figure 4A). After training, in the HIT-EM group, there were significant decreases in delta percent mean (Δ Mean) in anthropometric variables, namely, TSF -10.3% and AbdSF -22.8% (Figure 2E and Figure 2H), SSF -16.0% (Table 1), and systolic BP -11.9% (Figure 3B), and in metabolic variables, namely, FINS -22.8% and HOMA-IR -22.9% (Figure 4E and Figure 4H) respectively. In the HIT-NM group, there were significant decreases in anthropometric variables, i.e., TSF -6.8% (Figure 2E), SSF -18.9% (Table 1) and AbdSF -15.9% (Figure 2H); metabolic variables, i.e., FINS -22.7% and HOMA-IR -15.8% (Figure 4E and Figure 4H); and muscle performance variables, i.e., $1RM_{LE}$ +42.1% and $1RM_{UR}$ +25.0% (Table 2). A large statistical effect size was found for TSF in both the HIT-EM (-1.40; 90% CI = -2.17, -0.64) and HIT-NM group (-1.31; 90% CI = -1.80, -0.82) (Figure 2E), as well as for SSF in the HIT-NM group (-1.24; 90% CI = -1.55, -0.92) (Table 1).

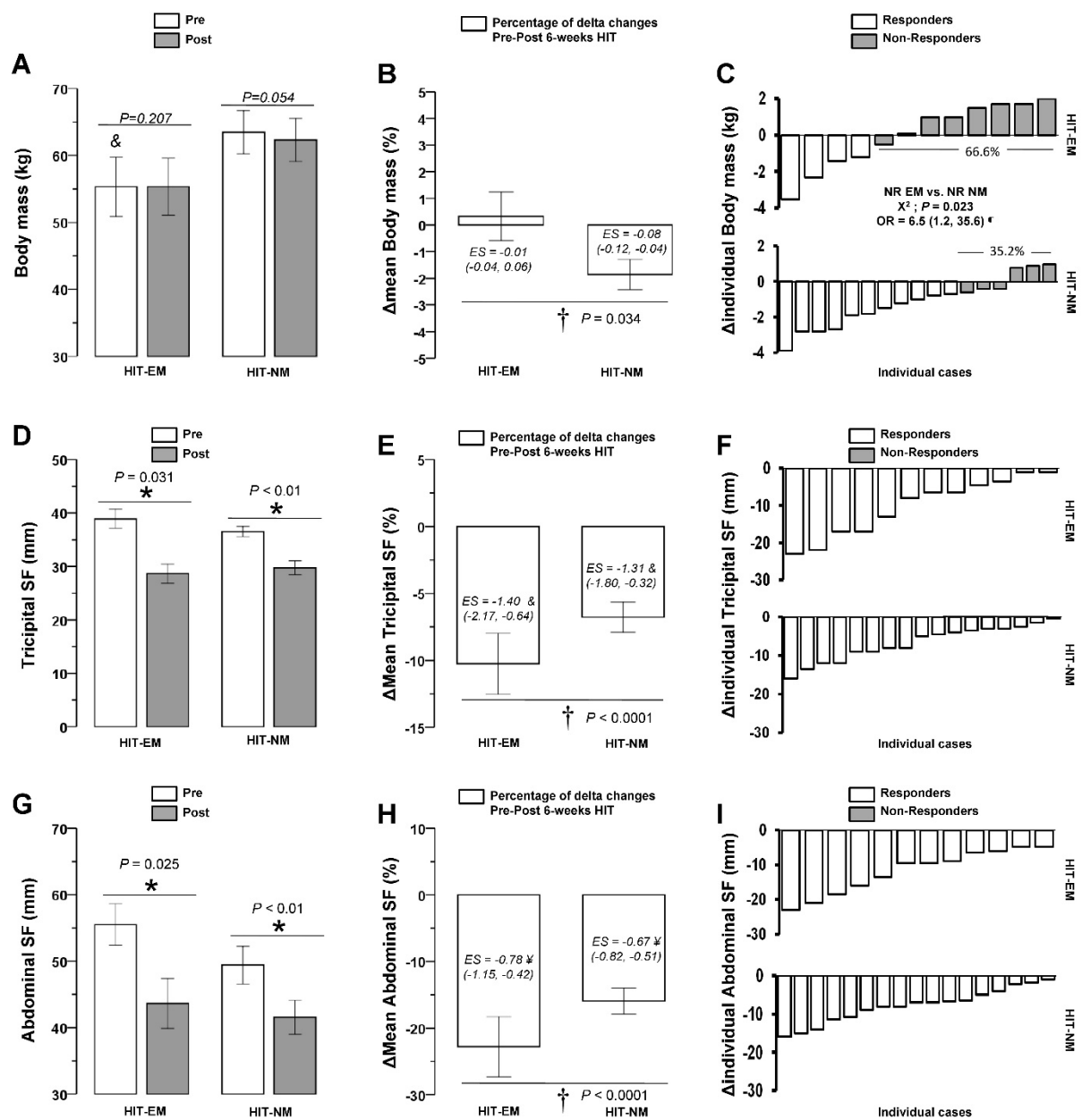


Figure 2. Pre-post changes, delta percent (Mean), and delta (individual) to body mass, tricipital, and abdominal skinfold after 6-weeks of HIT in insulin resistant schoolchildren. Footnote: Groups are described as: HIT-EM = high-intensity interval training early mature group, HIT-NM = high-intensity interval training early mature group. (*) Denotes significant pre-post changes intra-group at level $P<0,05$. (†) Denotes significant different between HIT-EM vs. HIT-NM group at level $P<0.05$.

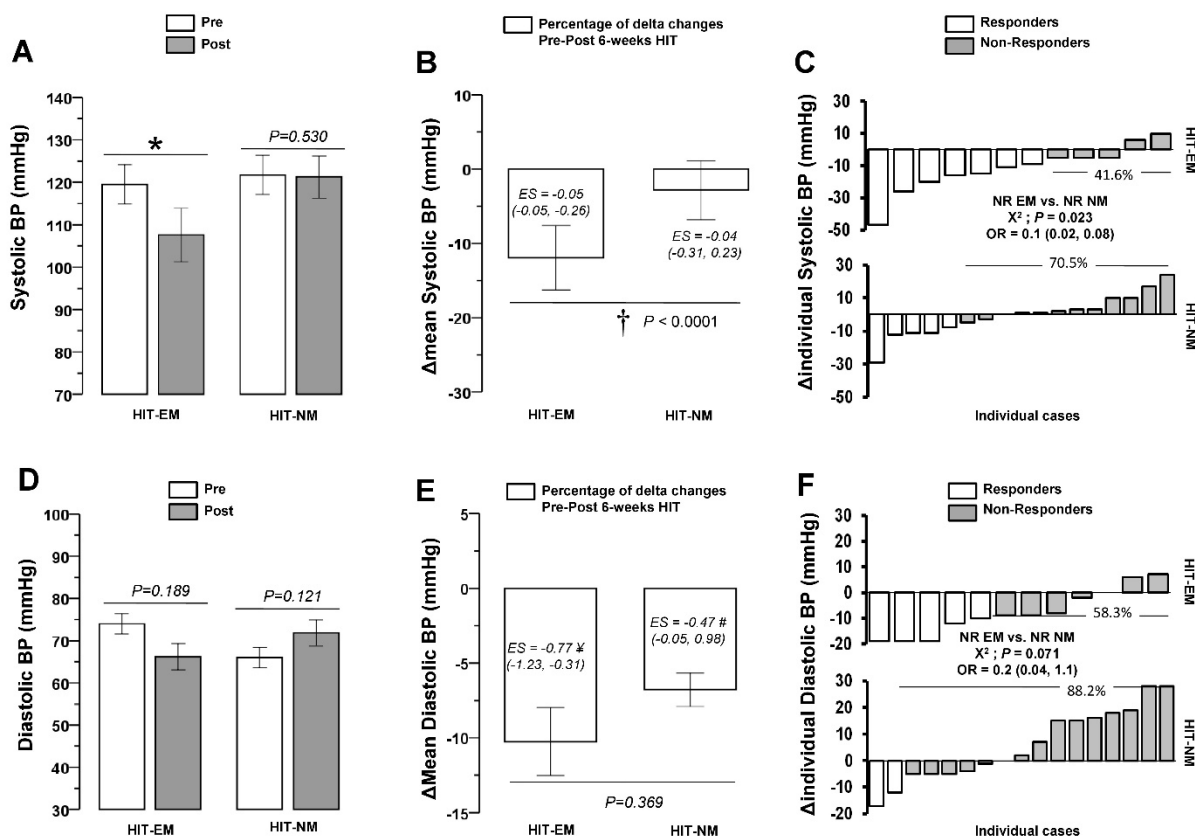


Figure 3. Pre-post changes, delta percent (Mean), and delta (individual) to systolic and diastolic blood pressure after 6-weeks of HIT in insulin resistant schoolchildren. Footnote: (*) Denotes significant pre-post changes intra-group at level $P < 0.05$. (†) Denotes significant different between HIT-EM vs. HIT-NM group at level $P < 0.05$.

Prevalence of non-responders in other body composition, cardiovascular, and strength performance co-variables

There were significant ($P < 0.05$) differences in the NR prevalence between groups in terms of decreased body mass, HIT-EM group 66.6% vs. HIT-NM group 35.2%, as well as decreased systolic BP, HIT-EM group 41.6% vs. HIT-NM group 70.5% (Figure 3C).

There were no significant differences in the prevalence of NR between groups in the other dependent co-variables tested (Table 4). There were no NR based on TSF or AbdSF in either group (Figure 2F and Figure 2I), including in $1RM_{LE}$ in the HIT-NM group (Table 4).

The risk of being a NR according to the OR was high (≥ 2 -fold) for the variables body mass, OR = 6.5, 95% CI 1.2, 36.6, $P = 0.023$ (Figure 2C); BMI, OR = 3.6, 95% CI 0.7, 17.4, $P = 0.096$; and $1RM_{LE}$, OR = 2.5, 95% CI 1.6, 4.0, $P = 0.728$ (Table 4), in the HIT-EM group vs. the HIT-NM group.

Table 4. Differences in the non-responder prevalence to improve body composition, blood pressure, metabolic, and performance parameters in children with insulin resistance after a HIT intervention.

Variable	Response Type	HIT-EM (N = 12)	HIT-NM (N = 17)	OR (95% CI) for NR	Pvalue HIT-EM vs. HIT-NM
Gender (♀ / ♂)		9 / 3	11 / 6		
Body composition					
Body mass index (% / n =)	NR R	66.7 (8) 33.3 (4)	35.3 (6) 64.7 (11)	3.6 (0.7 to 17.4) †	0.096
Waist circumference (% / n =)	NR R	33.3 (4) 66.7 (8)	35.3 (6) 64.7 (11)	0.9 (0.1 to 4.3)	0.913
Supra-iliac skinfold (% / n =)	NR R	8.3 (1) 91.7 (11)	5.9 (1) 94.1 (16)	1.4 (0.1 to 25.8)	0.798
Strength performance					
1RM _{LE} (% / n =)	NR R	8.3 (1) 91.7 (11)	0 (0) 100 (17)	2.5 (1.6 to 4.0) †	0.226
1RM _{UR} (% / n =)	NR R	41.7 (5) 58.3 (7)	35.3 (6) 64.7 (11)	1.3 (0.2 to 5.9)	0.728

HIT-EM = high-intensity interval training earlier matures group; HIT-NM = high-intensity interval training normal matures group; 1RM_{LE} = one maximum repetition strength test; 1RM_{UR} = one maximum repetition upper row strength test; OR = odds Ratios. NR = non-responders. R = responders. † Denote high risk (≥ 2 fold) to suffer a NR in HIT-EM vs. HIT-NM group.

Prevalence of non-responders in terms of metabolic variables

There were no significant ($P<0.05$) differences between the HIT-EM and HIT-NM groups in the NR prevalence according to decreased FGL (83.3% vs. 94.1%, $P=0.348$) (Figure 4C), to decreased FINS (33.3% vs. 41.2%, $P=0.668$) (Figure 4F), or HOMA-IR (25% vs. 35.3%, $P=0.555$) (Figure 4I).

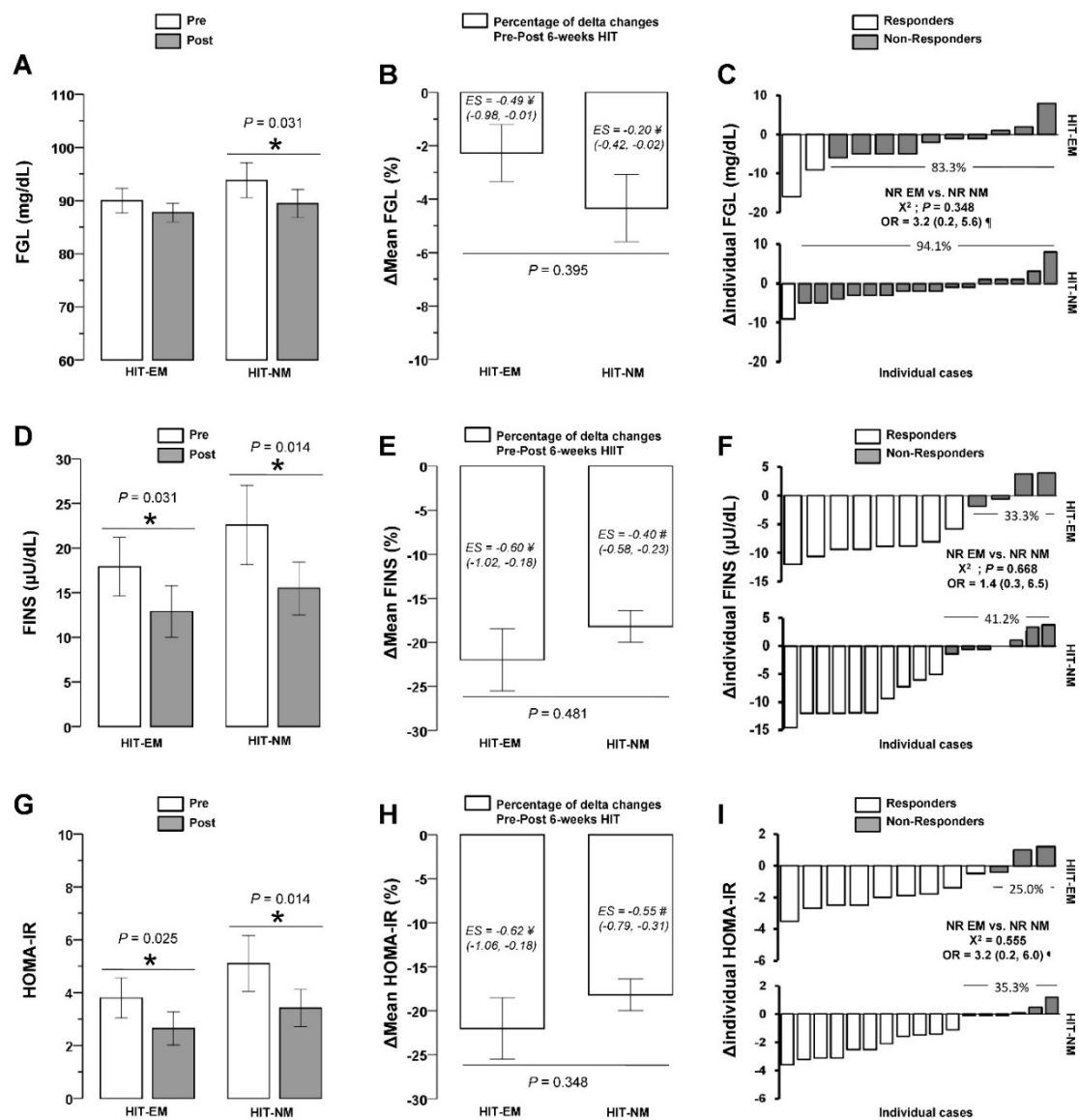


Figure 4. Pre-post changes (A,D,G), delta percent (mean) (B,E,H), and delta (individual) (C,F,I) of body mass, tricipital, and abdominal skinfold after 6-weeks of HIT in insulin-resistance schoolchildren. Groups are described as: HIT-EM, high-intensity interval training early maturation group; HIT-NM, high-intensity interval training normal maturation group. *Denotes significant pre-post intragroup changes at level $P < 0.05$. ‡Denotes significant differences between HIT-EM vs. HIT-NM groups at level $P < 0.05$. #Denotes ‘small’ statistical effect size at $P < 0.05$. §Denotes ‘moderate’ statistical effect size at $P < 0.05$. &Denotes ‘large’ statistical effect size at $P < 0.05$. ¶Denotes high risk of suffering a non-response.

Discussion

This study has four main results: *i*) there was no significant differences between children with EM and NM in the prevalence of NR based on improved metabolic profiles (fasting glucose, fasting insulin, HOMA-IR); *ii*) independent of the NR prevalence and of biological maturation (i.e., EM, NM), HIT was able to decrease fasting insulin and HOMA-IR in IR schoolchildren; *iii*) there were significant differences in the NR prevalence in terms of other body composition (body mass) and systolic BP co-variables; and *iv*) HIT promoted improvements in the other body composition (decreased skinfold), decreased systolic blood pressure, and muscular performance co-variables included in this study.

To the author's knowledge, there is no evidence regarding the prevalence of NR after HIT interventions in children with IR. In this study, HIT was able to reduce subcutaneous fat in both the HIT-EM and HIT-NM groups including TSF -10.3% vs. -6.8%, SSF -16.0% vs. -18.9%, and AbdSF -22.8% vs. -15.9%, respectively (Figure 2, and Table 1). These results are in accordance with previous HIT interventions (1 min work interval, 3 min recovery, 3-6 bouts, 12-weeks) in children that have reported a decrease in body mass of -2.7%, fat mass of -2.6%, and WC of -7% (Corte de Araujo et al., 2012). Unfortunately, these authors did not report the NR prevalence. Despite the fact that there are known differences in biological maturation between children of the same chronological age (Ortega et al., 2008), it remains unknown whether children with earlier vs. a normal maturation are more commonly NR to similar modes of training, such as HIT. Among the unknown effects of HIT on the NR prevalence, we found in this study that there were no NR in terms of decreased TSF or AbdSF in both the earlier and normal maturation groups (Figure 2). In this line, after 12-weeks of endurance training in adults, there was a NR prevalence according to decreased body mass and body fat of 3.3% and 13.3%, respectively (King et al., 2008). After 9-months of HIT (15-30 s, 2 bouts/10 min, at 80% of maximal aerobic power, treadmill/cycling), previous authors have shown a 7.2% prevalence of NR based on decreased WC and an 8.6% prevalence of NR in decreased total fat mass among subjects with metabolic syndrome (Gremeaux et al., 2012). It is worth noting that only 2-weeks of HIT in adults has led to decreases in WC of -2.3% (Whyte, Gill, & Cathcart, 2010). In addition, it appears that HIT rapidly leads to benefits regarding improved body composition markers such as skinfold measurements in children, and these findings are in accordance with studies in adults. Thus, it appears that in a sample size (i.e., ~10 subjects) regularly used in exercise interventions and with a high compliance, HIT has an important contribution to decreasing fat; this finding has been reported after HIT regimens, in which adrenergic mechanisms post-exercise have an important role (Boutcher, 2011).

Additionally, we observed that the HIT-NM group showed a higher prevalence of NR in terms of decreased systolic BP, at 70.5%, than the HIT-EM group, which showed a 41.6% prevalence of NR (Figure 3C). Other studies have shown an NR prevalence of 60.9% in decreased systolic BP, and of 59.1% in decreased DBP after 5-months of endurance (65-80% VO_2peak , walking/jogging), strength (8-12 repetitions per set, 8 exercises, 70-85% of 1RM, 3 days/week), or concurrent training (Moker et al., 2014). Regarding the lack of evidence on the potential influence of the start of biological maturation on promoting more/less NR in terms of glucose control among children under a HIT regime at school, the earlier maturation group in this study apparently had a lower risk of NR in terms of decreased systolic BP after this mode of training (Figure 3C). We found a significant decrease in systolic BP of -11.9%, which was greater than the decrease in the other HIT-NM group of -2.8%. We speculate that HIT rapidly promotes angiogenic factors to increase capillarization, which provides an advantage that is translated to their limited muscle mass (although we did not assess this variable) compared with that of children with normal maturation who apparently present more IR. Similarly, a NR prevalence in decreased systolic BP of 12.2% has been reported after endurance training (30-50 min/session, 3 days/week, 55-75% VO_2max , 20-weeks) in a study assessing a wide sample of subjects (Claude Bouchard et al., 2012). Other HIT-based studies in adults have reported a NR prevalence in terms of decreased diastolic BP of 61.5%, and our study is in accordance with this finding, reporting a value of 58.8% (Higgins et al., 2015).

Subjects with both earlier and normal maturation showed decreases in FINS of -22.8% and -22.7% and in HOMA-IR of -22.9% and -15.8%, respectively, after the intervention (Figure 4), and there were no differences between groups in the prevalence of NR in terms of decreased FGL, FINS or HOMA-IR (Figure 2), respectively. There were no cases of NR in TSF or AbdSF (Figure 2) in either group or in 1RM_{LE} in the HIT-NM group (Table 4), in which all subjects were R. Thus, both TSF and AbdSF show a high sensitivity to change after HIT interventions. Some authors have reported a NR prevalence of 8.4% in decreased FINS; however, these studies examined adults and the effects of endurance training (Claude Bouchard et al., 2012). To the author's knowledge, there are no studies reporting the prevalence of NR after HIT in children and how earlier/normal maturation could influence the response after training. Based on our results of decreases in HOMA-IR in both the earlier and normal maturation groups, of -35.7 and -26.9%, respectively, we confirm that HIT is a powerful mode of training for sedentary IR children and additionally that HIT results in few or no NR cases in this study including a standard sample size (i.e., ~10-20 subjects).

This suggests that neither an earlier nor a normal start of biological maturation plays a role in the NR prevalence as measured by decreased FGL, FINS, and HOMA-

IR in children with IR. Moreover, we did not find differences in the NR prevalence based on increased $1RM_{LE}$ or $1RM_{UR}$ in either intervention group (Table 4). We also observed a high risk (≥ 2 -fold) of being a NR in the HIT-EM, at 8.3%, vs. the HIT-NM group, at 0%, but this included only 1 case. We observed significant increases in $1RM_{LE}$ and $1RM_{UR}$ in the HIT-NM group of +42.1 and +25.0%, respectively (Table 2). We can state in general that HIT is able to increase the strength performance of lower limbs by cycling when the effort is tailored to 8-10 points on the modified Borg scale and the load progressively adjusted to maintain this qualitative short-term effort.

Strengths and limitations

A strength of this study was that we included a sample of 10-20 subjects in each group, and this size is frequently used in training interventions (Ziemann et al., 2011). We also reported pre-post changes, as well as the effect size and OR of NR for each group. Additionally, we assessed other body composition, cardiovascular, metabolic and muscle performance co-variables regularly used in training studies with children. One limitation was that we did not control for additional exercise after each training session, but this information was recorded each week in children and parents to maintain similar baseline conditions of exercise and diet. Additionally, among children, it is widely known that they have an increased energy expenditure, and we presume that part of the differences in the training-induced changes between subjects in the HIT-EM vs. HIT-NM groups were due to discrepancies in hormonal and molecular processes that we did not assess (due to were not the aim of this study).

Conclusion

In conclusion, our results suggest that independent of biological maturation, NR to HIT occurred in the majority of variables, with the exceptions of TSF, AbdSF, FINS, and HOMA-IR. Thus, HIT is associated with significant improvements in several metabolic, body composition, blood pressure, and performance parameters independent of their early/normal maturation or the prevalence of NR. There were no differences in the prevalence of NR to metabolic variables between groups of IR schoolchildren, however, there were significant differences in the NR prevalence in other body composition (body mass) and cardiovascular (systolic BP) co-variables included.

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Chapter 5

Metabolic effects of resistance or high-intensity interval training among glycaemic control-nonresponsive children with insulin resistance

* **Cristian Álvarez**, Rodrigo Ramírez-Campillo, Robinson Ramírez-Vélez, Cristian Martínez, Mauricio Castro-Sepúlveda, Alonso Alonso-Martínez and Mikel Izquierdo. Metabolic effects of resistance or high-intensity interval training among glycaemic control-nonresponsive children with insulin resistance. International journal of obesity 2018, (42)79-87.

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Chapter 6

Inter-individual responses to different exercise stimuli among insulin-resistant women

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Chapter 7

Concurrent training and prediabetes comorbidities: An analysis of non- responders using clinical cut-off points

***Cristian Álvarez**, Rodrigo Ramírez-Campillo, Alejandro Lucía, Robinson Ramírez-Vélez, and Mikel Izquierdo. Concurrent training and prediabetes comorbidities: An analysis of non-responders using clinical cutoff points. Submitted.

Concurrent training and prediabetes comorbidities: an analysis of non-responders using clinical cutoff points

Abstract

Background/aims: To investigate the effects of a 20-weeks CT intervention on cardiovascular risk factors such as body composition, blood pressure and lipid profile among adult women with hyperglycemia. A secondary aim was to report prevalence of NR for the different study outcomes. **Methods:** Physically inactive overweight/obese and hyperglycemic adult women (age = 42 ± 6 years; BMI = 30.9 ± 4.8 kg/m²) were randomly assigned to a 20-weeks CT intervention group or a control (non-exercise) group (CG), ($N = 14$ /group). Co-morbidities indices for body composition, blood pressure and metabolic were assessed before and after the 20-weeks intervention. **Results:** Beyond a decrease in fasting glucose (-4 mg/dL on average, $P = 0.05$), significant benefits of CT were found for mean values in adiposity (body mass -1.3 kg, $P = 0.026$ and WC -4.0 cm, $P < 0.0001$) and lipid profile (total cholesterol -12 mg/dL, $P = 0.038$; LDL-cholesterol -11 mg/dL, $P = 0.022$; HDL-cholesterol +4 mg/dL, $P = 0.003$; and triglycerides -25 mg/dL, $P < 0.0001$), were these outcomes do not showed changed in control group.. At the individual level, the proportion of responders (R) and non-responders (NR) were the following: for WC (CT 14% and 86%; CG 0% and 100%), for systolic blood pressure (CT 36% and 14.2%; CG 14% and 7%), for diastolic blood pressure (CT 0% and 0%; CG 7% and 14%), for total- (CT 14% and 29%; CG 7% and 28%), LDL- (CT 21% and 36%; CG 0% and 43%), HDL-cholesterol (CT 14% and 50%; CG 14% and 57%) and triglycerides (CT 21% and 14%; CG 0% and 43%), respectively. **Conclusions:** In addition to its benefits on glucose homeostasis, a 20-week CT intervention for women with prediabetes can decrease abdominal obesity and improve lipid profile in 'mean' terms, as well as enhance the clinical status of some individuals (*i.e.*, those who are R) from a 'high' to a 'normal'/'low' cardiovascular risk after training.

Keywords: glucose control, cardiovascular risk factors, exercise training, type 2 diabetes mellitus

Introduction

When exercise training is adequately supervised and adherence is high, it has a therapeutic effect in individuals with prediabetes or type 2 diabetes mellitus (T2DM) (Little et al., 2011; Johansen et al., 2017). This is especially important when considering that oral hypoglycaemic drugs are frequently prescribed for patients who have not yet exceeded the recommended clinical cut-off score for starting this type of medication (Colberg et al., 2010), but do already have 1+ comorbidity upon which exercise can also be useful, such as excess adiposity (Álvarez, 2013), high blood pressure (Tuomilehto et al., 2001), or an unhealthy blood lipid profile (Qasim et al., 2011).

Many of the cardiometabolic risk factors associated with T2DM can be improved or ameliorated with weight control and diet, as well as with regular exercise. Indeed, the beneficial effects of high-intensity interval (HIT) and resistance (RT) training on IR have been extensively studied at the level of skeletal muscle and adipose tissue (Zanuso et al., 2017). In this regard, HIT has become an increasingly popular training modality for reducing such risk factors, based on a number of metabolic improvements including fat reduction, increased lipid oxidation and improved insulin sensitivity. Accordingly, HIT can decrease 24 h average glucose concentration by -13% on average (Little et al., 2011), fasting glucose ~14% (Alvarez et al., 2016), waist circumference (WC, -2.4 cm) (Whyte et al., 2010), fat mass -5.6% (Álvarez et al., 2017), or systolic blood pressure (SBP, -6 mmHg) (Whyte et al., 2010) in adults with poor glucose control. In turn, RT combined with weight loss can decrease WC ~7 cm, SBP ~7 mmHg, or fasting glucose ~5% (Dunstan et al., 2002). Metabolic improvements comparable to those aforementioned have also been reported after concurrent training (CT), which is RT combined with either endurance training (ET) or HIT (Sigal et al., 2007; Church et al., 2010).

Notwithstanding the irrefutable clinical benefits of exercise in general, there is a known inter-individual variability in the response to different exercise interventions (Bouchard et al., 2012b), including CT (Stephens et al., 2015). Whereas some individuals, the so-called ‘responders’ (R) improve their metabolic profile after a training intervention (e.g., a decrease in fasting glucose) others, the ‘non-responders’ (NR) show no response or even an opposite response (Boulé et al., 2005). From a statistical viewpoint, a non-response for a given variable is a lack of difference between a control and a treatment condition. The NR phenomenon has been shown in a non-negligible proportion of participants in exercise intervention studies, for instance, in 4–9% of adults at risk for T2DM (Phillips et al., 2017) or in 21% of patients with T2DM (Stephens et al., 2015). Consequently, the use of personalized medicine to prescribe tailored exercise interventions could be a valuable treatment approach for individuals identified

as NR. The purpose of this study was to investigate the effects of a 20-week CT intervention on cardiovascular risk factors such as body composition, blood pressure and lipid profile among adult women with hyperglycaemia. A secondary aim was to report the prevalence of NR for the different study outcomes.

Material and methods

Participants and study design

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Family Healthcare Center *Tomás Rojas*, Chile. All volunteers read a detailed description of the study and provided their written informed consent to participate.

We performed a 20-weeks, randomized controlled trial on overweight/obese women diagnosed with hyperglycaemia by our research team. The patients underwent a structured history, medical record review at the Family Healthcare Center *Tomás Rojas*, and had a physical examination by a physician for the assessment of eligibility criteria. Eighty-three adult women [41 ± 6 years, body mass index (BMI) 26–35 kg/m²] participated in a first screening stage consisting of a telephone call with explanations regarding the study aims; those who agreed to participate were called for a second stage where the study was explained in detail.

Eligibility criteria were the following: a) age between 30 and 59 years, b) not living in a rural area, c) physical activity levels [as assessed by the International Physical Activity Questionnaire (IPAQ) previously validated in the Chilean population] < 600 metabolic equivalents (MET)·min/week (Seron et al., 2010), d) non-involvement in regular exercise during the previous 6-months, e) fasting glucose of 100–125 mg/dL (ADA, 2017), and f) 1+ values above (or below for HDL-cholesterol) normal cutoffs for: body composition [*i.e.*, WC > 80 cm, which denotes ‘high cardiovascular risk’ in South American individuals (Alberti et al., 2009)]; blood pressure [Systolic (SBP) and diastolic blood pressure (DBP) of 130–139 mmHg and 85–90 mmHg, respectively, denoting ‘high blood pressure’, or SBP and DBP >140 mmHg and 90 mmHg, respectively, denoting ‘hypertension’] (Mancia et al., 2013); or blood lipid profile (*i.e.*, total cholesterol > 200 mg/dL, LDL-cholesterol > 140 mg/dL, HDL-cholesterol < 50 mg/dL, or triglycerides \geq 150 mg/dL) (Alberti et al., 2009). Exclusion criteria were: a) cardiovascular contraindications to exercise, b) history of stroke, asthma or chronic obstructive pulmonary disease, c) muscle-skeletal disorders, and d) smoking. A compliance rate to the exercise program \geq 70% was required for the participants in the intervention group to be included in the statistical analyses.

In the second stage, 83 women were screened and 43 were finally excluded due to the following reasons: aged 60 + years ($N = 17$), living in rural areas ($N = 2$), taking oral antihyperglycemic drugs ($N = 4$), muscle-skeletal disorder ($N = 1$), history of stroke ($N = 4$), asthma ($N = 7$), or performing regular PA ($N = 8$). Thus, in the third stage of allocation, 40 subjects were randomized using a computer-generated random

assignment in a 1:1 ratio to a CT intervention or control group during a 20-weeks period. The study design is shown in Figure 1.

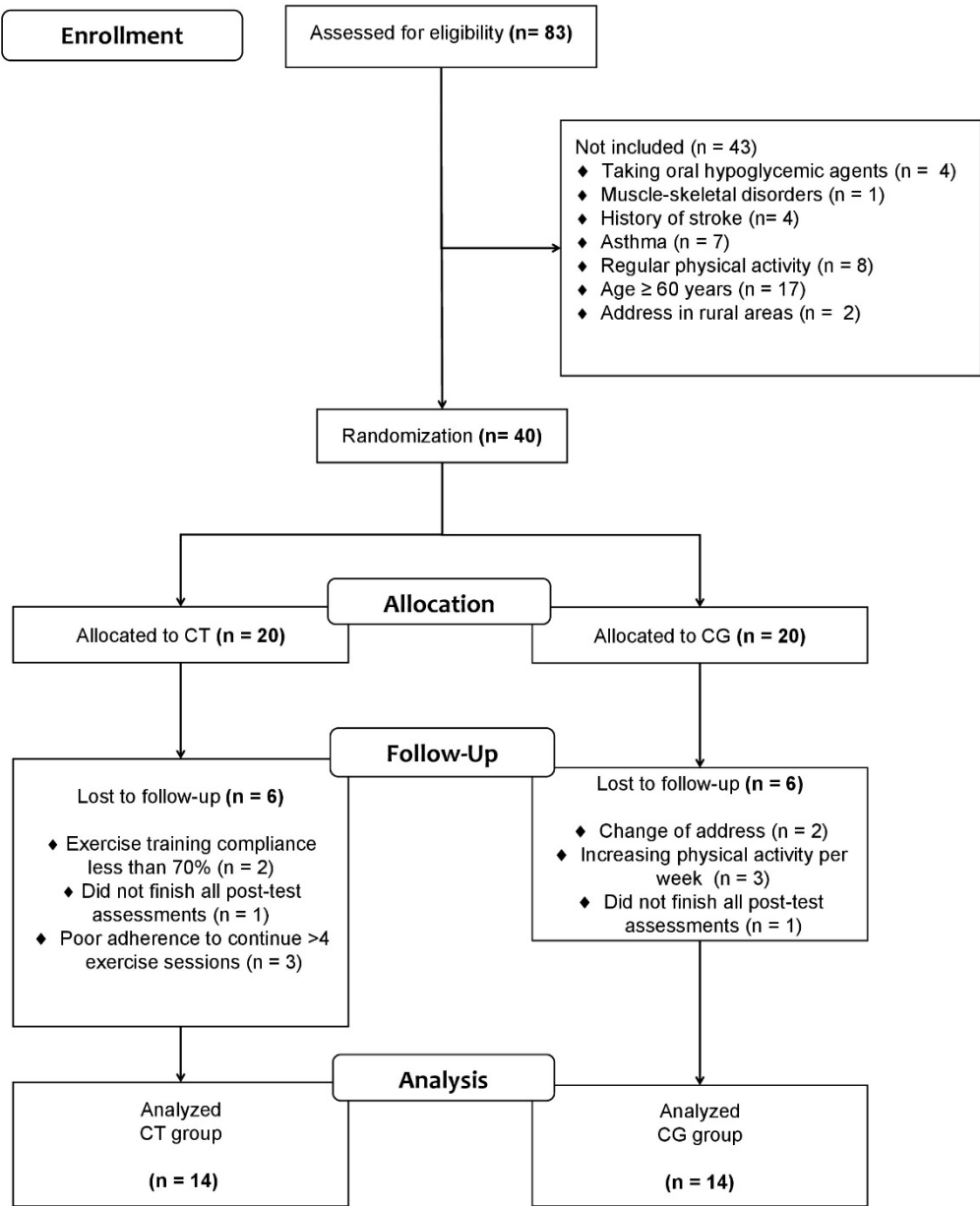


Figure 1. Study design.

Metabolic assessments

Blood samples (4 mL) were drawn (in the morning, after a 10–12 h fast) before and after the intervention. The samples were placed on ice and then centrifuged at $2,000 \times g$ for 5 minutes at 4 °C. Plasma samples were immediately transferred to pre-chilled microtubes and stored at -20 °C for subsequent analysis. Plasma glucose, total cholesterol and triglycerides were analysed enzymatically using standard kits (Wiener Lab Inc., Rosario, Argentina) on an automatic analyser (Metrolab2300 Plus™, Metrolab Biomed Inc., Buenos Aires, Argentina). HDL-cholesterol was analyzed using an enzymatic method after phosphotungstate precipitation (Demacker et al., 1997) and LDL-cholesterol was calculated using the Friedewald formula (Friedewald et al., 1972).

Body composition

Body mass (kg) was measured (to the nearest 0.1 kg) using a professional scale (Health o Meter™ Professional, Sunbeam Products Inc., Chicago, IL). WC was measured with a calibrated measuring tape (Hoechstmass™, Sulzbach, *Germany*) in millimeters and centimeters, using anatomical landmarks—midpoint between the lower border of the rib cage and the iliac crest, taking the length at the end of expiration, with participants standing and wearing only undergarments. Fat (expressed as percentage of total body mass) and lean mass (kg) were assessed in the post-prandial state (after a normal breakfast but without caffeine, and with no previous exercise) using tetrapolar electrical bioimpedance (50 kHz, < 500 µA) on a digital scale (Omron HBF-INT™, Omron Healthcare Inc., Lake Forest, IL). Subjects were asked to remove jewelry and watches to increase assessment precision, were previously instructed for not drink water at least 1 h before the assessment and the average of three measurements was used.

Blood pressure

SBP and DBP were recorded by an automatic monitor (Omron HEM 7114™, Omron Healthcare Inc.) in triplicate (2-minute interval between measurements) after 15 minutes of rest, with the subjects in a seated position and with both feet resting on the floor, according to standard procedures (Mancia et al., 2013). Resting heart rate was measured using a chest monitor (ProTrainer 5™, Polar Electro Inc., Kempele, Finland) after subjects had rested in the supine position for at least 15 min.

Endurance performance

The six-minute walking test (6Mwt) was performed (between 09.00 and 11.00 in the morning) in an indoor sports court (100-meter track) after a 5-minute warm-up consisting of low-intensity walking and slow movements involving the knee and ankle joints. The subjects were instructed to walk as fast as possible with a steady pace, but not to run similar with previous studies (Metz et al., 2017).

Concurrent training

Prior to the CT intervention, all subjects were familiarized (during 3 sessions) with the training protocols. The CT intervention included 3 weekly sessions of both ET and RT. The core part of each session included RT followed by ET exercises (for 50 and 30 minutes, respectively) and was preceded and followed by a 5-minute warm-up and cool-down with callisthenic movements.

The RT part included 8 exercises (biceps curl, flex/extension of triceps, shoulder press, half squat, gastrocnemius flex/extension, abdominal crunches, lower back concentric exercise) performed with dumbbells [at no more than 10–20% of the one-maximum repetition (1RM)] or own subjects' body mass (data not shown). Each exercise was executed following 1 minute of work by concentric/eccentric voluntary actions, followed by 1 minute of passive recovery. For the ET part, each subject was involved in walking/running at no more than 70% of their predicted maximum heart rate (Karvonen, 1988). Accordingly, how this ET part was applied in each subject depended on the initial individual fitness levels [*i.e.*, from walking at 'low' (in the most unfit subjects), 'moderate', or 'vigorous' intensity, to running at 'low', 'moderate', or 'vigorous' intensity (in the fittest)]. Exercise heart rate intensity was continuously monitored (ProTrainer 5™, Polar Electro Inc.) and each walking/running speed was gradually increased each week during the intervention period to always maintain the ET exercise intensity. All the sessions were supervised by fitness instructors and were performed at the same time of the day (between 9.00 and 12.00 in the morning). All subjects in the CT group had a good exercise tolerance, and none reported any injury or major health problem associated with the intervention. Exercise compliance averaged ~80%.

Definition of responders/non-responders by clinical cutoff points

For WC, blood pressure, fasting glucose, HDL-cholesterol and triglycerides, responders were those showing a positive change over a clinically relevant cutoff value from an altered to a normal value in the South American population; for example, a decrease in WC from a value denoting high cardiovascular risk (≥ 80 cm) to one (< 80 cm) denoting low cardiovascular risk (Alberti et al., 2009)). For SBP, responders were those showing a change from 'high blood pressure' to normotensive, or from hypertension to 'high blood pressure'. For HDL-cholesterol, responders were those showing increases from values < 50 mg/dL to ≥ 50 mg/dL, and for triglycerides a decrease from ≥ 150 mg/dL to < 150 mg/dL. Subjects not showing these changes were classified as non-responders, or non-classified (*i.e.*, those showing baseline values within normal limits). For the remaining endpoints (body mass, fat mass percentage, lean mass, resting heart rate, fasting glucose, total cholesterol, LDL-cholesterol and 6Mwt test, we used standard laboratory cutoffs as there are no established normative cut-offs for separating high from low cardiovascular risk patients. Thus, for total cholesterol, a value < 200 mg/dL denotes normocholesterolemia whereas ≥ 200 mg/dL indicates hypercholesterolemia; for LDL-cholesterol, a value $< \text{or } \geq 130$ mg/dL denotes normolipidemia or dyslipidaemia, respectively, or simply the positive or negative values from '0' as beneficial/detrimental changes in body mass, BMI, fat mass percentage, lean mass, resting heart rate, and the 6Mwt.

Definition of the prevalence of non-responders

Using previously established criteria in exercise interventions (Bouchard et al., 2012a), the prevalence of non-responders to exercise training of the subjects were categorized as responders (R), and non-responders (NR) using the technical error measurement (TE), by the following equation:

$$TE = SD_{diff} / \sqrt{2}$$

Where SD_{diff} is the variance (standard deviation) of the difference scores observed between the 2 repeats of each test. A NR was defined as an individual who failed to demonstrate an increase or decrease (in favour of beneficial changes) that was greater than 2 times the TE away from zero. A change beyond 2 times the TE means that there is a high probability (i.e. 12 to 1 Odds) that this response is a true physiological adaptation beyond what might be expected to result from technical and/or biological variability. Thus the TE were the following (body mass, 0.300 kg x 2; WC, 0.50 cm x 2; fat mass, 1.03% x 2; lean mass, 0.410 kg x 2; SBP, 4.01 mmHg x 2; DBP, 2.49 mmHg x 2; heart rate at rest, 2.72 b/min x 2; total cholesterol, 6.7 mg/dL x 2; LDL-cholesterol, 6.2 mg/dL x 2; HDL-cholesterol, 2.5 mg/dL x 2; and triglycerides, 12.3 mg/dL x 2).

Statistical analyses

Data are presented as the mean \pm SD (Tables) or SEM (Figures). Normality and homoscedasticity assumptions for all data were analysed using the Shapiro-Wilk and Levene's tests, respectively. Student's *t* test was used to identify differences at baseline. An ANCOVA was conducted (using height as co-variable) for body mass and LDL-cholesterol based on baseline differences. A repeated measures, two-way (group, time) was applied to assess occurrence of an actual training effect [i.e., $P < 0.05$ for the interaction (group \times time) for the different study outcomes]. The Bonferroni *post hoc* test was applied to test differences among groups. Additionally, Cohen's *d* test was used to detect effect size, using the threshold values of 0.20, 0.60, 1.2, and 2.0 for small, moderate, large, and very large effects, respectively (Hopkins et al., 2009), with 95% confidence intervals (CI). All statistical analyses were performed with SPSS statistical software version 18 (SPSSTM Inc., Chicago, IL). The alpha level was fixed at $P < 0.05$ for statistical significance.

Results

The final sample size for statistical analysis was 28 subjects: $N = 14$ for each of CT (43 ± 6 years, $BMI = 29.8 \pm 3.9$ kg/m²) and CG (40 ± 6 years, $BMI = 32.0 \pm 5.8$ kg/m²) groups (Table 1).

Table 1. Results of study endpoints by group.

	Intervention CT		Within-group	Cohen d Effect Size (95%CI)	CG		Within-group	Cohen d Effect Size (95%CI)	Between-group CT vs CG Baseline†	Between-group CT vs CG Post†
	Pre	Post	Δ _{mean}		Pre	Post	Δ _{mean}			
N =		14				14				
Age (y)		43 ± 6				40 ± 6				
Height (m)		1.53 ± 0.05				1.56 ± 0.07			P = 0.058	
Body composition										
BMI (kg/m ²)	29.8 ± 3.9	29.6 ± 3.5	-0.2 (-0.6%)	-0.05 (-0.19, 0.09)	32.0 ± 5.8	32.1 ± 6.0	+0.1 (+0.3%)	0.01 (-0.03, 0.05)	P = 0.246	P = 0.186
Normal n (%)	0 (0%)	1 (7%)	+1 (7%)		1 (7%)	1 (7%)	0 (0%)			
Overweight n (%)	8 (57%)	8 (57%)	0 (0%)		4 (28.5%)	4 (29%)	0 (0%)			
Obesity n (%)	6 (43%)	5 (36%)	-1.0 (7%)		9 (64.2%)	9 (64%)	0 (0%)			

Prevalence of non-responders after concurrent training by clinical cut-off points in prediabetes

Hip circumference (cm)	89.0 ± 8	88.0 ± 9	-1 (-1.1%)	-0.01 (0.00, 0.01)	91.0 ± 9	92.0 ± 7	+1 (1.0%)	-0.01 (0.00, 0.01)	<i>P</i> = 0.683	<i>P</i> = 0.680
Waist-to-hip ratio	1.09 ± 0.07	1.04 ± 0.08 ^{‡‡}	-0.05 (-4.5%)	-0.53 [#] (-0.88, -0.18)	1.10 ± 0.06	1.11 ± 0.07	+0.01 (+0.9%)	0.06 (-0.07, 0.18)	<i>P</i> = 0.496	<i>P</i> = 0.037
<i>CVR by waist circumference</i>										
§ ↑High-CVR <i>n</i> (%)	14 (100%)	12 (86%)	-2 (-14%)		14 (100%)	14 (100%)	0 (0%)			
↓Low-CVR <i>n</i> (%)	0 (0%)	2 (14%)	+2 (+14%)		0 (0%)	0 (0%)	0 (0%)			
<i>CVR by blood pressure</i>										
¶ Normotensive <i>n</i> (%)	9 (64%)	12 (86%)	+3 (+22%)		11 (79%)	11 (79%)	0 (0%)			
§ ¶¶ High BP <i>n</i> (%)	4 (29%)	1 (7%)	-3 (-21%)		1 (7%)	2 (14%)	+1 (+7%)			
§ Grade 1 HTN <i>n</i> (%)	1 (7%)	1 (7%)	0 (0%)		2 (14%)	1 (7%)	-1 (-7%)			
HR rest (b/min)	74 ± 6	73 ± 5	-1.0 (-1.3%)	-0.25 [#] (-0.60, 0.10)	68 ± 7	70 ± 8	+2.0 (+2.9%)	0.22 [#] (0.00, 0.44)	<i>P</i> = 0.012	<i>P</i> = 0.217
<i>Metabolic glucose control</i>										
§ FGL (mg/dL)	109 ± 12	105 ± 11 [‡]	-4.0 (-3.6%)	0.31 [#] (-0.72, 0.10)	109 ± 14	112 ± 17	+3.0 (+2.7%)	0.25 [#] (-0.06, 0.55)	<i>P</i> = 0.391	<i>P</i> = 0.019
<i>CVR by blood lipid profile</i>										
High- TC <i>n</i> (%)	6 (43%)	4 (29%)	-2 (-14%)		4 (29%)	4 (29%)	0 (0%)			
High- LDL-C <i>n</i> (%)	8 (57%)	5 (36%)	-3 (-21%)		4 (29%)	4 (29%)	0 (0%)			
§ Low- HDL-C <i>n</i> (%)	9 (64%)	7 (50%)	-2 (-14%)		10 (71%)	8 (57%)	-2 (14%)			
§ High- TG <i>n</i> (%)	5 (36%)	3 (21%)	-2 (-14%)		6 (43%)	6 (43%)	0 (0%)			
<i>Endurance performance</i>										
6Mwt (m)	566 ± 57	622 ± 36 [‡]	+56.0 (+9.8%)	1.03 [§] (0.29, 1.77)	561 ± 80	559 ± 83	-2.0 (-0.3%)	-0.03 (-0.15, 0.08)	<i>P</i> = 0.848	<i>P</i> = 0.014

Data are presented as mean ± SD, or number of subjects and percentage. HTN, hypertension; 6Mwt, 6-minute walking test; BMI, body mass index; CT, concurrent training group; CG, control group; CVR, cardiovascular risk; TC, total cholesterol; LDL-C, low density lipids; HDL-C, high density lipids; TG, triglycerides. (↑) Denotes high-cardiovascular risk by a waist circumference (WC) ≥ 80 cm in South American women. (↓) Denotes low-cardiovascular risk by a WC < 80 cm in South American women. (¶) Systolic BP < 130 mmHg/diastolic BP < 84 mmHg. (¶¶) Systolic BP 130-139 mmHg/diastolic BP 85–89 mmHg. (§) All these are outcomes are components of the metabolic syndrome. (‡) Denotes significant training-induce changes at *P*<0.05. (‡‡) Denotes significant training-induce changes at *P*<0.0001. (†) Between-group analyses were performed with Student's *t* test with level *P*<0.05 as a significant difference. Bold values denote significant differences between groups at level *P*≤0.05. (#) Denotes ‘small’ Cohen *d* effect size. (&) Denotes ‘moderate’ Cohen *d* effect size.

Baseline

Significant ($P<0.05$) differences between groups were identified at baseline for body mass (Figure 2A), resting heart rate (Table 1), and LDL-cholesterol (Figure 4D).

Mean changes after the intervention

Body composition described as ‘mean’ and ‘individual’ changes are shown in Table 1 and Figure 2A–L. The CT group showed a significant reduction in mean body mass after the intervention (Figure 2A), with a decrease $\Delta_{\text{mean}} -1.3$ kg, $P=0.026$ (Figure 2B), whereas a non-significant increase of $\Delta_{\text{mean}} +0.4$ kg was observed in the CG (Figure 2C). No changes were found in either group for mean values of BMI after the intervention (Table 1). Waist-to-hip ratio significantly decreased ($\Delta_{\text{mean}} -0.05$ cm, $P<0.0001$) in the CT group, with a moderate effect size (Table 1). In addition, WC decreased significantly in the CT group (Figure 2D), with a decrease $\Delta_{\text{mean}} -4.0$ cm, $P<0.0001$ (Figure 2E), whereas a non-significant increase of $\Delta_{\text{mean}} +1.0$ cm was found in the CG (Figure 2F). Both fat mass and lean mass changed in beneficial terms in the CT group (-1.3% , Figure 2H, and $+0.4$ kg, Figure 2K, respectively); however, these changes were non-significant ($P>0.05$) in mean terms for both outcomes (Figure 2G and Figure 2J). The CG showed a non-significant increase ($\Delta_{\text{mean}} +0.3\%$ and $\Delta_{\text{mean}} +0.1$ kg) in both outcomes (Figure 2I and Figure 2L).

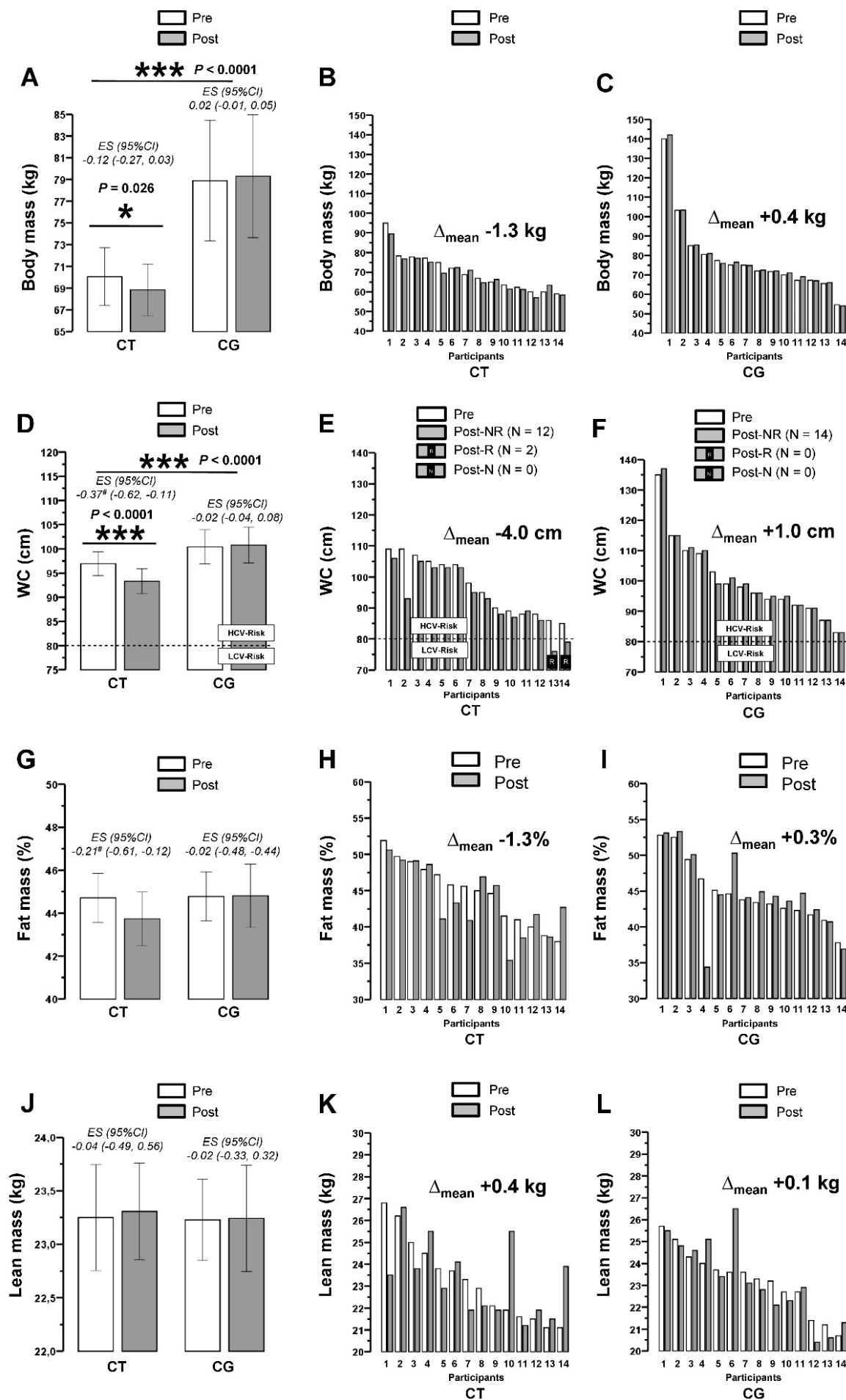


Figure 2. Mean and individual changes in four body composition outcomes (A, B, C; body mass, D, E, F; Waist circumference, G, H, I; Fat mass, and J, K, L; Lean mass) in hyperglycaemia women participants of 20-weeks of two different exercise regimes. (CT) Concurrent training group, (CG) Control group. (Post-NR) Denotes cases that do not change positively to the health of clinical baseline diagnosed after intervention. (Post-R) Denotes cases that change positively to the health of clinical baseline diagnosed after intervention. (Post-N) Denotes cases that do not classified as some cardiovascular risk at baseline. (Δ_{mean}) Denotes the mean of delta changes between pre-post test including all the participants. (ES) Cohen d effect size calculated at P<0.05. (*) Denotes significant changes within group at P≤0.05. (***) Denotes significant changes within group at P<0.0001. (#) Denotes 'small' statistical effect size at P<0.05.

Mean SBP (Δ_{mean} -6 mmHg, Figure 3B) tended to decrease with the CT intervention but without reaching statistical significance (Figure 3A), whereas this outcome was non-significantly increased in the CG (Figure 3C). No significant changes were observed to DBP (Figure 3D), despite increases in mean (Δ_{mean} +3 mmHg, Figure 3D). Moreover, no significant changes were found in resting heart rate between groups after the intervention (Table 1).

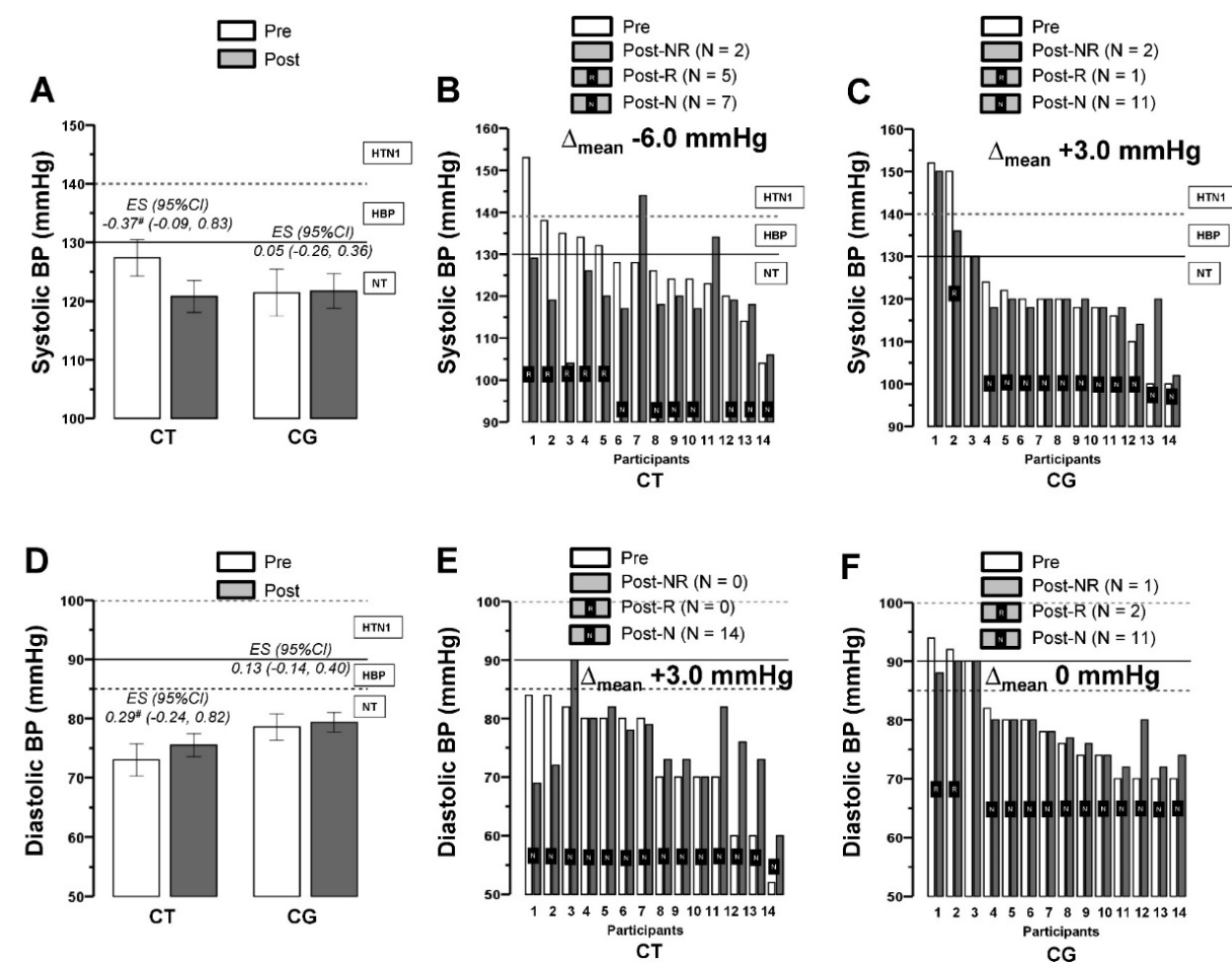


Figure 3. Mean and individual changes in cardiovascular outcomes (A, B, C; Systolic BP, D, E, F; Diastolic BP), in hyperglycaemic women participants of 20-weeks of two different exercise regimes. (CT) Concurrent training group, (CG) Control group. (Post-NR) Denotes cases that do not change positively to the health of clinical baseline diagnosed after intervention. (Post-R) Denotes cases that change positively to the health of clinical baseline diagnosed after intervention. (Post-N) Denotes cases that do not classified as some cardiovascular risk at baseline. (Δ_{mean}) Denotes the mean of delta changes between pre-post test including all the participants. (ES) Cohen *d* effect size calculated at $P < 0.05$. (#) Denotes 'small' statistical effect size at $P < 0.05$

Fasting glucose decreased significantly ($P < 0.05$) after the 20-week intervention in the CT group (Δ_{mean} -4 mg/dL on average, $P = 0.039$), but not in the CG (Table 1). Similarly, significant training-induced mean effects were found for total cholesterol, LDL- and HDL-cholesterol, and triglycerides in (Figure 4A, D, G, J, respectively), showing a decrease for total cholesterol (Δ_{mean} -12, $P = 0.038$ Figure 4B), LDL-cholesterol (Δ_{mean} -11, $P = 0.022$ Figure 4E), HDL-cholesterol (Δ_{mean} +4, $P = 0.003$ Figure 4H), and triglycerides (Δ_{mean} -25 mg/dL, $P < 0.0001$ Figure 4K). These changes in the lipid profile were significantly different in all four variables at $P < 0.0001$ (Figure 4A-K). No significant changes in these parameters were found in the CG.

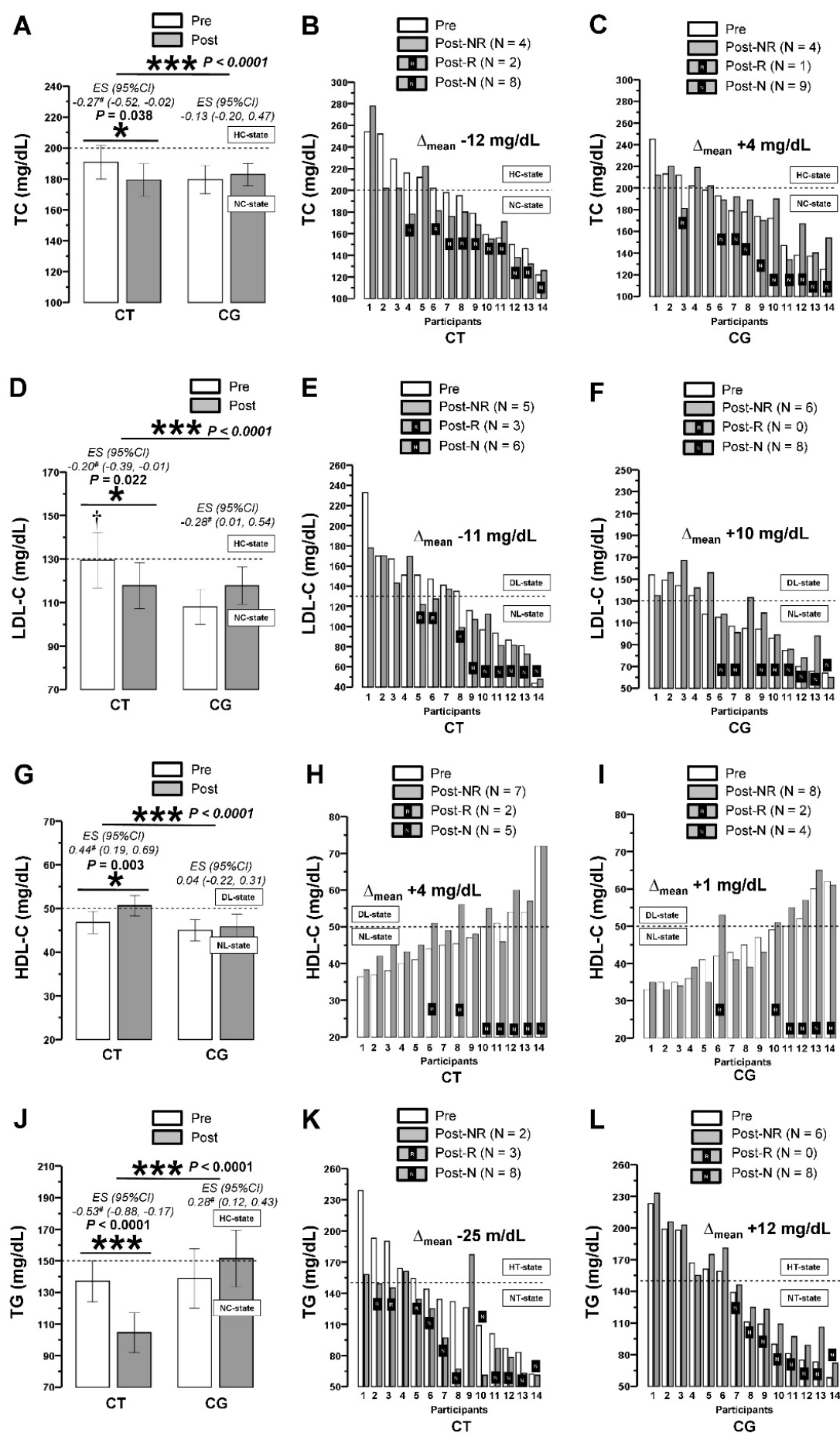


Figure 4. Mean and individual changes in four metabolic outcomes (A, B, C; total cholesterol, D, E, F; low-density lipids, G, H, I; high-density lipids, and J, K, L; triglycerides) in hyperglycaemia women participants of 20-weeks of two different exercise regimes. (CT) Concurrent training group, (CG) Control group. (Post-NR) Denotes cases that do not change positively to the health of clinical baseline diagnosed after intervention. (Post-R) Denotes cases that change positively to the health of clinical baseline diagnosed after intervention. (Post-N) Denotes cases that do not classified as some cardiovascular risk at baseline. (Δ_{mean}) Denotes the mean of delta changes between pre-post test including all the participants. (ES) Cohen *d* effect size calculated at $P < 0.05$. (HC-state) Denotes hypercholesterolemia state. (NC-state) Denotes normocholesterolemia state. (DL-state) Denotes dyslipidaemia state. (NL-state) Denotes normolipidemia state. (HT-state) Denotes hypertriglyceridemia state. (NT-state) Denotes normotriglyceridemia state. (†) Denotes significant differences versus CG. (*) Denotes significant changes within group at $P \leq 0.05$. (***) Denotes significant changes within group at $P < 0.0001$. (#) Denotes 'small' statistical effect size at $P < 0.05$.

Similarly, the mean performance in the 6Mwt ($\Delta_{\text{mean}} +56$ m) test improved with CT intervention ($P<0.0001$), whereas no change was found in CG group (Table 1).

Responders and non-responders by clinical cut-off points

Regarding body composition, two subjects were responders in the CT group, changing from a 'high' to a 'low' cardiovascular risk status from baseline to post-training, whereas 12 subjects were non-responders for WC (Figure 2E). All 14 subjects from the CG were non-responders (Figure 2F).

Five subjects in the CT group were R, 2 NR, and 7 were 'non-classified' (*i.e.*, normal levels at baseline) (N) for SBP, changing the R from hypertension stage 1 (1 subject) to normotensive, or from having high blood pressure (4 subjects) to being normotensive. In the CG, 1 subject was R (changing from hypertension to high blood pressure state), 2 were NR, and 11 N. For DBP, all 14 subjects in the CT group had normotensive values at baseline, being all N (Figure 3E). Two subjects in the CG were R changing from a hypertensive to a normotensive state, 1 was NR, and 11 N, after the intervention period (Figure 3F).

Regarding blood lipids, 2 subjects in the CT group were R for a change from hypercholesterolemia to normocholesterolemia, 4 subjects were NR, and 8 were N (Figure 4B). In the CG, 1 subject was R, 4 were NR and 9 were N (Figure 4C). In the CT group 3 were R for a change in LDL-cholesterol, 5 were NR, and 6 had non-altered levels at baseline, being N (Figure 4E); 6 subjects in the control group were NR and the other 8 had non-altered values at baseline (Figure 4F). For HDL-cholesterol, in the CT group there were 7 NR, 2 R, and 5 non-classified subjects, whereas in the control group 8 subjects were NR, 2 were R and 4 were non-classified (Figure 4H, I). Finally, in the CT group, 3 subjects were R for triglycerides, 2 were NR, and 8 were non-classified (Figure 4K). By contrast, all subjects in the CG were NR (Figure 4L).

Prevalence of non-responders

Regarding body composition, there were different non-responders prevalence rates between the intervention and control group for body mass (28.5% and 85.7% in the CT and CG, respectively), WC (7.1% and 92.9%), fat mass percentage (64.2% and 92.8%), and lean mass (78.6% and 85.7%) (Figure 5A–K).

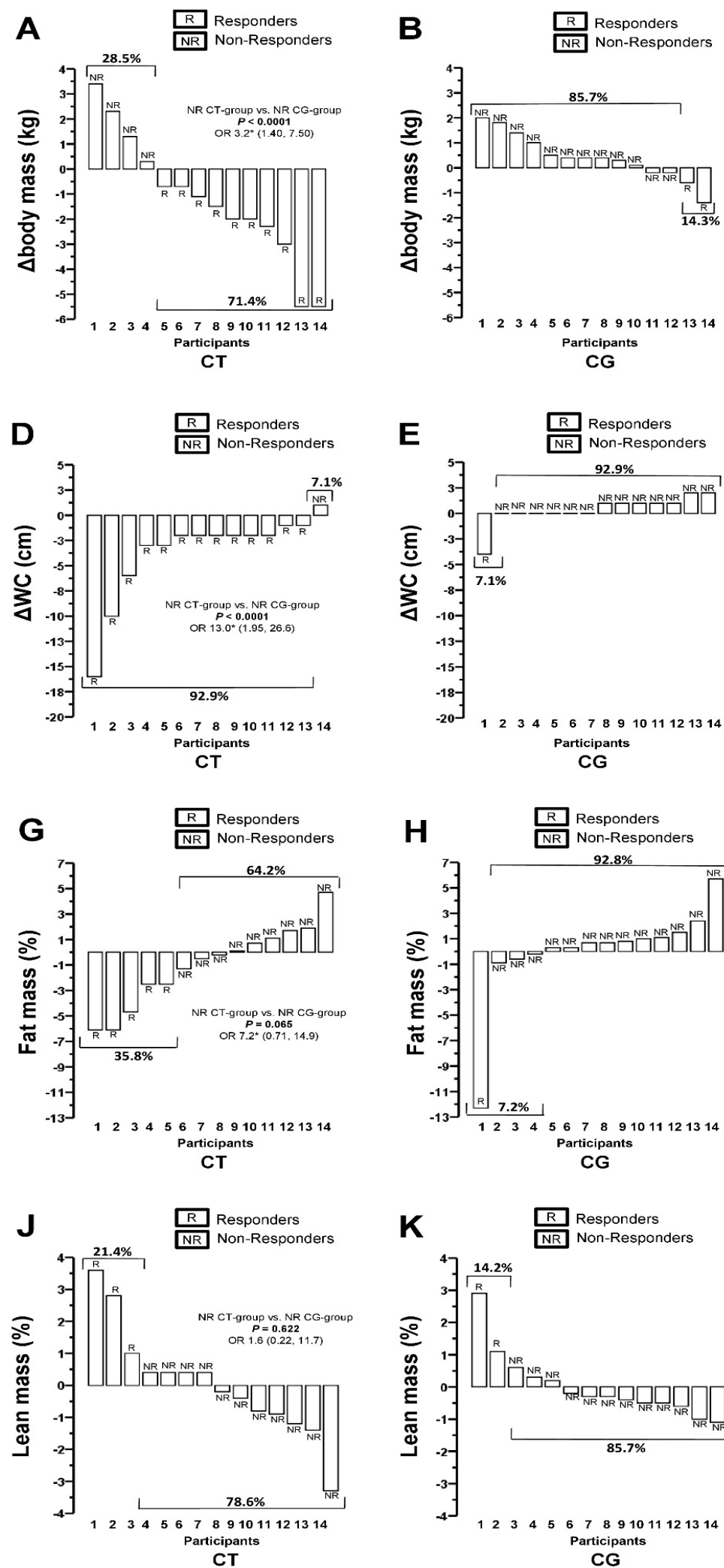


Figure 5. Delta individual changes in four body composition outcomes (A, B; body mass, C, D; Waist circumference, E, F; Fat mass, and G, H; Lean mass) in hyperglycaemic women participants of 20-weeks of two different exercise regimes. (CT) Concurrent training group, (CG) Control group. (OR) Odds ratios with 95%CI.

Prevalence rates of non-responders for SBP were (50.0% and 92.8% in the CT and CG, respectively), DBP (85.7% and 92.8%), and resting heart rate (78.6 and 100%) (Figure 6A–F).

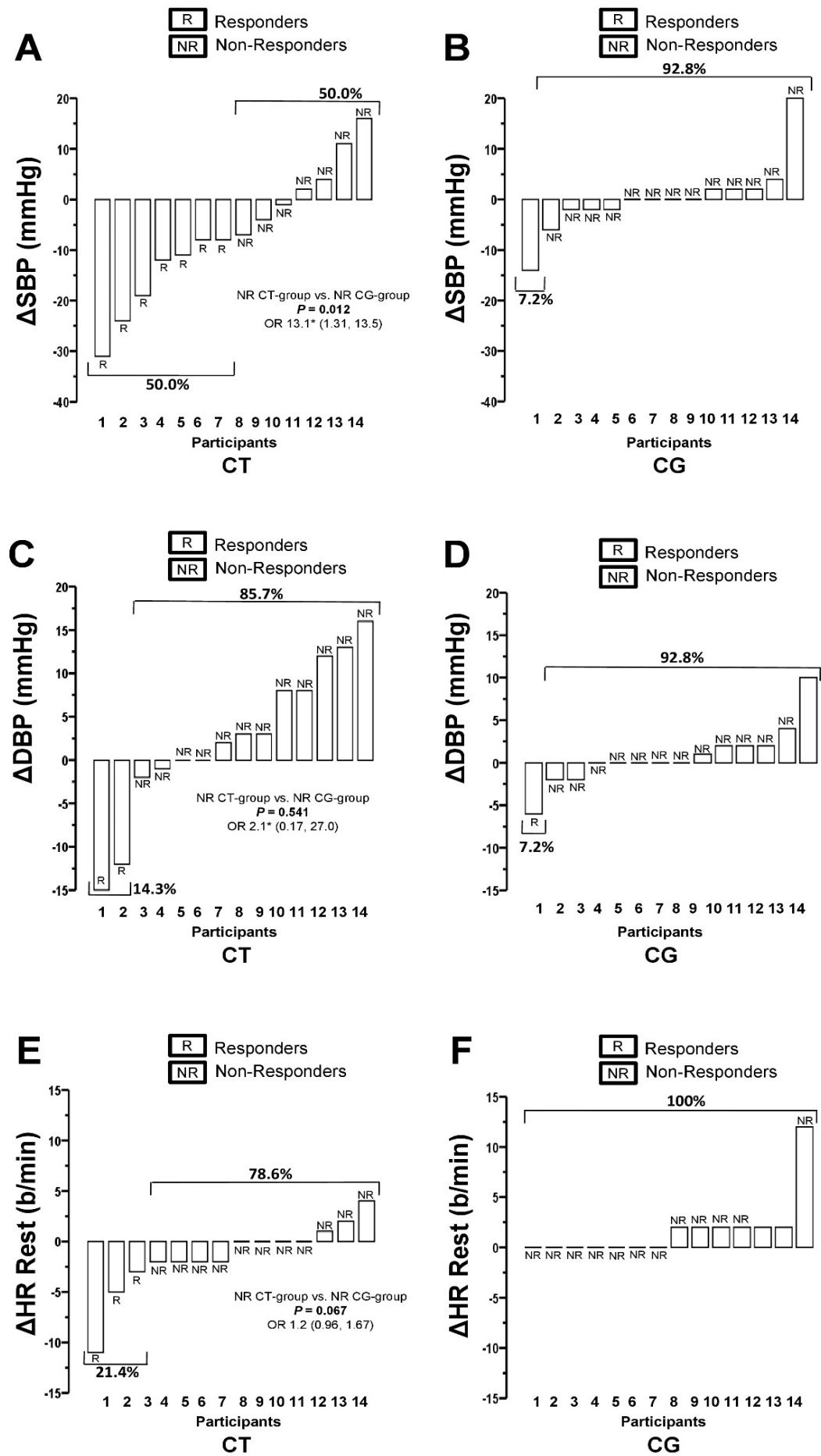


Figure 6. Delta individual changes in three cardiovascular outcomes (A, B; systolic, C, D; diastolic blood pressure, E, F; heart rate at rest) in hyperglycaemic women participants of 20-weeks of two different exercise regimes. (CT) Concurrent training group, (CG) Control group.

Prevalence rates of non-responders for blood lipids were total cholesterol (50.0% and 85.8% of in the CT and control group, respectively), LDL-cholesterol (57.2% and 92.8%), HDL-cholesterol (57.2% and 71.5%), and triglycerides (57.2% and 100%) (Figure 7A–K).

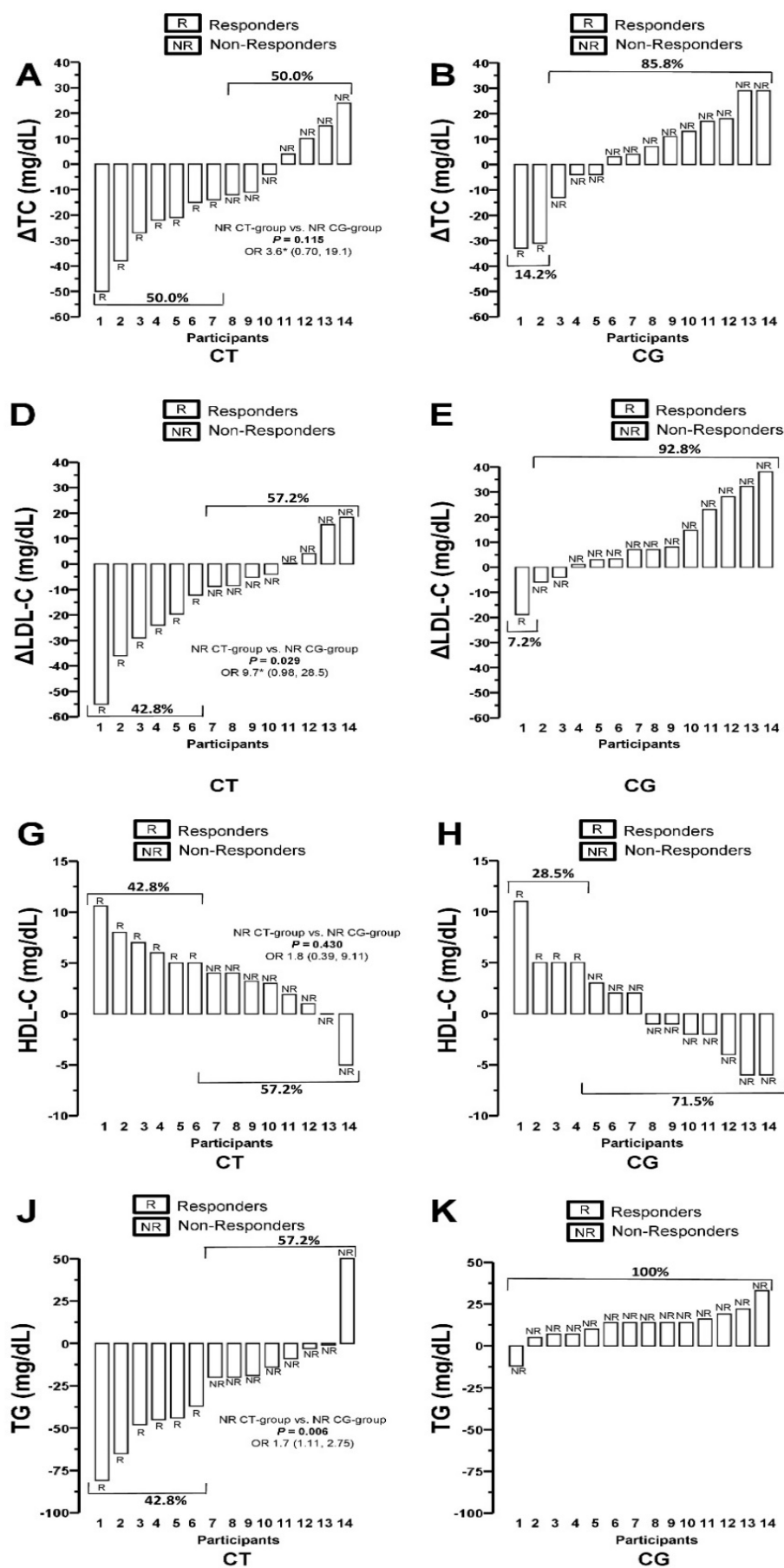


Figure 7. Delta individual changes in four metabolic lipid profile outcomes (A, B; total cholesterol, C, D; low-density lipids, E, F; high-density lipids, and G, H; triglycerides) in hyperglycaemic women participants of 20-weeks of two different exercise regimes. (CT) Concurrent training group, (CG) Control group.

Discussion

Our results show that a CT intervention results in a reduction of co-morbidities in terms of abdominal obesity and cardiovascular risk in adult women with hyperglycaemia by decreasing WC and improving lipid profile in 'mean' terms. At the individual level, after CT, some subjects changed their status from a 'high' to a 'low' cardiovascular risk in terms of WC, while others changed from hypertension to either high blood pressure or normotension, or from high blood pressure to normotension, and others changed from hypercholesterolemia/dyslipidaemia to normocholesterolemia. Overall, there were ~30%, 50% and 20% of individuals in the CT exercise group who showed no change/adverse response for body composition, blood pressure, and metabolic lipid profile, respectively, after the 20-weeks CT intervention.

Although there is evidence supporting the benefits of CT for improving glucose control in T2DM patients, there is yet no clear indication of the ability of this exercise modality to combat T2DM-associated comorbidities. A 12-months lifestyle intervention for T2DM patients that included exercise training (5–6 ET sessions of 30-60 minute duration plus 2–3 RT sessions per week) and diet (Johansen et al., 2017) decreased fasting glucose (-7.8 mg/dL on average) and changed several other parameters such as abdominal fat (-0.81 kg), lean mass (+0.62 kg), SBP/DBP (-1.5/-1.4 mmHg), triglycerides (-8.4 mg/dL), and VO_{2peak} (+14.5%). Along this line, after an 8-week CT intervention for T2DM patients (60 minutes/session, including ET [cycling/treadmill] plus RT at 55–85% of 1RM), Maiorana et al. found decreases in fasting glucose (-40 mg/dL on average), resting heart rate (-4 beats/min), waist-to-hip ratio (-1.3%) and fat mass (-0.8%), but no changes in lipid profile or blood pressure (Maiorana et al., 2002). In other studies, low-to-moderate-intensity ET was found to be as effective as moderate-to-high-intensity training in a T2DM population (Hansen et al., 2009), whereas high-intensity ET was found to be more effective for improving glycaemic control (Dunstan et al., 2002).

After 20-weeks of CT (ET 15–20 minutes of treadmill/cycling at 60% of the age-predicted maximum heart rate plus RT 7 exercises, 2–3 sets of 7–9 repetitions, on three days/week) Sigal et al., reported that, besides improvements in glycaemic control (as indicated by levels of glycated haemoglobin), there were also training-induced decreases in body mass (-2.6 kg), WC (-4 cm), body fat (-5%) and SBP (-2 mmHg), together with an improved lipid profile (+1.1, -4 and -22 mg/dL for HDL-cholesterol, LDL-cholesterol and triglycerides, respectively), but no changes were found for lean mass and DBP (Sigal et al., 2007). Church et al. showed that CT [2 sessions/week of ET (at 50–80% of VO_{2peak}) plus RT] in T2DM patients elicited improvements in both

glucose control, as reflected in glycated haemoglobin levels (-0.34%, 95%CI; -0.64, -0.03) and total body (-1.6 kg) and fat mass (-1.8 kg), and WC (-2.7 cm), but lean mass did not change (Church et al., 2010).

We found decreases in markers of obesity, with average decreases in body mass (-1.3 kg) and fat mass (-1.3%) similar to those reported by other authors using a shorter, apparently more time-efficient, intervention (*i.e.*, 8-weeks vs. 20-weeks here) (Maiorana et al., 2002). Conversely, the results we found for WC are similar to those reported by other authors using also a 20-weeks CT intervention (Sigal et al., 2007). A novelty of our approach, however, is the reporting of responders and non-responders using the clinical baseline as a criterion.

Several biological pathways can explain the protective role of CT against cardiometabolic disease risk. Muscle contractions, via increased cytoplasmic calcium concentration or membrane depolarization, can induce ~4-fold increases in the recruitment and/or translocation of glucose transporter protein-4 (GLUT-4) to the plasma membrane due to the activation of 5'-AMP-activated protein kinase (AMPK) (Jorge et al., 2011). Given that 85% of the total body glucose disposal occurs in the muscle tissue, the aforementioned effects of muscle contractions on GLUT-4 likely play a crucial role in glucose homeostasis (DeFronzo et al., 1985). Muscle contractions also increase glucose uptake and improve insulin sensitivity in skeletal muscle (Richter and Hargreaves, 2013). In addition to this, CT can improve skeletal muscle and adipose tissue insulin resistance by reducing total and abdominal body fat (Baar, 2014; Murach and Bagley, 2016), as well as through alterations in the rate of secretion of tumour necrosis factor- α (decreased) and adiponectin (increased) from the adipose tissue to the bloodstream (Strasser et al., 2012; Samjoo et al., 2013). Other training effects include increased muscle mass, enhanced activity of glycolytic and tricarboxylic acid cycle enzymes, and increased mitochondrial function (Donges et al., 2013; Baar, 2014).

It is not uncommon that hyperglycaemic patients are physically inactive and are prescribed oral hypoglycaemic drugs despite not strictly fulfilling all the criteria for receiving such treatment (*i.e.*, fasting blood glucose < 126 mg/dL or blood glucose < 140 mg/dL after an oral glucose tolerance test), but nevertheless having comorbidities such as abdominal fat obesity, high blood pressure and altered lipid profile (Nolan et al., 2015). It is thus important to implement exercise interventions in these individuals, not only for improving glucose homeostasis, but also for attenuating the aforementioned comorbidities and cardiovascular risk in general.

Because hypoglycaemic drugs do not act on T2DM-related comorbidities and given the fact that taking a medication usually makes patients think that lifestyle is not

so important as they are overall ‘protected’ by the drug, CT interventions appear suitable for pre-diabetic individuals.

Strengths and limitations

Our study is not without its limitations, such as the different duration of the ET and RT parts of the sessions (30 and 50 min, respectively), which might have biased the results owing to a stronger emphasis on RT. On the other hand, a strength of our study is that it is the first to test whether a 20-weeks CT intervention impacts T2DM-related cardiovascular risk factors (excess adiposity, high blood pressure or dyslipidaemia) in adult women with prediabetes. Another strength was that the intervention had good adherence. Finally, we reported identified responders and non-responders for each of the study outcomes.

Conclusion

In conclusion, in addition to its benefits on glucose homeostasis, a 20-weeks CT intervention for women with prediabetes can decrease abdominal obesity and improve lipid profile in 'mean' terms, as well as changing the clinical baseline of some individuals (*i.e.*, those who are responders) from a 'high' to a 'normal'/'low' cardiovascular risk after training.

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Chapter 7

Main results, conclusions, practical applications and future perspectives

Main results, conclusions, practical applications and future perspectives

Study 1 (Chapter 2)

The aim of this study was to investigate the effects and prevalence of NR to HIT and RT in adult woman with insulin resistance on glucose control parameters

Result 1: There were no differences in the NR prevalence between HIT and RT for decreasing fasting glucose (16.6 vs. 29.4%), fasting insulin (11.1 vs. 11.7%), and HOMA-IR (11.1 vs. 11.7%) respectively to each group; however, there were significant differences in other body composition (body mass, BMI, tricipital skinfold, fat, and muscle mass), cardiovascular (heart rate at rest, diastolic blood pressure), and performance co-variables included ($1RM_{BC}$, $1RM_{LE}$, $1RM_{SP}$, $1RM_{UR}$) after intervention.

Conclusion 1: 12-weeks of HIT and RT have similar effects and NR prevalence to improve glucose control variables; however, there is different NR prevalence in other anthropometric, cardiovascular, strength and endurance performance measurements in insulin resistance adult woman.

Practical application 1: To choose the most appropriate exercise mode such as HIT or RT in adult women with IR where both have benefits decreasing the IR levels, it is important to clarify which (including glucose control parameters) others body composition, cardiovascular, or strength outcomes it is relevant to improve, in order to avoid more NR.

Future perspectives 1: Future research in this area should include a) epigenetics measurements, b) to include other mode of training as concurrent or endurance training.

Study 2 (Chapter 3)

The aim of this study was to assess the effects of HIT and the prevalence of NR in adult women with higher and lower levels of insulin resistance.

Result 2: There were significant differences in the prevalence of NR between the H-IR and L-IR groups for fasting glucose (25 vs. 95%) and fasting insulin (25 vs. 60%) but not for HOMA-IR (25 vs. 45%).

Conclusion 2: Independent of the “magnitude” of the cardiometabolic disease (i.e., higher vs. lower insulin resistance), no differences were observed in the NR prevalence with regard to improved HOMA-IR or to body composition, cardiovascular, and muscle performance co-variables after 10-weeks of HIT in sedentary adult women. This research demonstrates the protective effect of HIT against cardiometabolic disease progression in a sedentary population

Practical application 2: In order to decrease the insulin resistance levels of adult woman, the HIT exercise mode can be equally effective in both contrasts of this metabolic alteration.

Future perspectives 2: Future research in this area should include a) epigenetics measurements, b) to include other mode of training as resistant, concurrent or endurance training.

Study 3 (Chapter 4)

The aim of this study was to compare the effects and prevalence of NR to improve the IR level (by HOMA-IR), as well as to other body composition, cardiovascular, and performance co-variables, between early (EM) and the normal maturation (NM) of insulin-resistance schoolchildren after 6-weeks of HIT.

Result 3: There were no significant differences between groups in the prevalence of NRs based on FGL, FINS, and HOMA-IR. There were significant differences in NRs prevalence to decrease co-variables body mass (HIT-EM 66.6% vs. HIT-NM 35.2%) and SBP (HIT-EM 41.6% vs. HIT-NM 70.5%). A high risk of NR cases was detected for FGL, and HOMA-IR. Additionally, both HIT-EM and HIT-NM groups showed significant decreases in TSF, SSF, and AbdSF skinfold, and similar decreases in fasting insulin and HOMA-IR. The HIT-EM group showed significant decreases in SBP. The HIT-NM group showed significant increases in $1RM_{LE}$ and $1RM_{UR}$.

Conclusion 3: Although there were no differences in the prevalence of NR to metabolic variables between groups, other NR differences were found to body mass and SBP, suggesting that body composition and cardiovascular parameters can be playing a role in the NR prevalence after HIT. These results were displayed with metabolic, body composition, blood pressure, and performance improvements independent of an early/normal maturation or the prevalence of NR.

Practical application 3: Despite that, HIT is a power strategy for decreasing the IR levels of children, the factor of biological maturation can play a role eliciting more/less NR after HIT in anthropometric and cardiovascular parameters.

Future perspectives 3: Future research in this area should include a) epigenetics measurements, b) to include other markers of glucose control such as the oral glucose tolerance test, and c) to include other exercise modes such as endurance, resistant and concurrent training.

Study 4 (Chapter 5)

The aim of this study was to examine those potential ‘mediators’ to the effects of 6-weeks of RT or HIT training on glucose control parameters in physically inactive schoolchildren with IR. Secondly, we also determined both training-induced changes and the prevalence of responders (R) and non-responders (NR) to decrease the IR level.

Result 4: Mediation analysis revealed that waist circumference could explain more the effects (decreases) of HOMA-IR in physically inactive schoolchildren under RT or HIT regimes. The one-maximum repetition leg-extension was correlated with the change in HOMA-IR ($\beta = -0.058$; $P=0.049$). Furthermore, a change in the waist circumference fully mediated the dose-response relationship between changes in the leg extension strength and HOMA-IR ($\beta' = -0.004$; $P=0.178$). RT or HIT were associated with significant improvements in body composition, muscular strength, blood pressure and cardiometabolic parameters irrespective of improvement in glycaemic control response. Both glucose control RT-R and HIT-R (respectively), had significant improvements in mean HOMA-IR, mean muscular strength leg-extension and mean measures of adiposity

Conclusion 4: The improvements in the lower body strength and the decreases in waist circumference can explain more the effects of the improvements in glucose control of IR schoolchildren in R group after 6-weeks of RT or HIT, showing both regimes similar effects on body composition or muscular strength independent of inter-individual metabolic response variability.

Practical application 4: In IR schoolchildren, where the main aim is to decrease the IR levels, by the simple measurement of waist circumference screening can be possible to correlate also decreases in the HOMA-IR marker.

Future perspectives 4: Future studies should include genetic/epigenetic measurements testing in those NR specific proteins related with no HOMA-IR decreases.

Study 5 [Accepted] (Chapter 6)

The aim of this study was to investigate which among 20-cardiometabolic and performance outcomes do and do not respond to high-intensity interval training (HIT), resistant training (RT), or concurrent training (CT) in IR adult women. A secondary aim was to report the training-induced changes and the prevalence of NR.

Result 5: Considering all outcomes, the lowest number of total non-responses for one or more variables was found in the RT group, followed by the CT and HIT groups. Individuals in the CG group were classified as non-responders for almost all the variables. Moreover, there were several significant changes in body composition and metabolic parameters, including fasting glucose (HIT: -5.7, RT -5.1 mg/d); fasting insulin (HIT:-0.6, RT -0.6 μ U/mL) and HOMA-IR (HIT:-0.3, RT -0.4), in addition to improvements in cardiovascular and performance parameters. Also, there were significant differences among groups in the prevalence of NR for the variables where a non-response was detected

Conclusion 5: Overall, the study suggests that independent of the mode of training including volume and frequency, RT has an important ability to reduce the prevalence of non-response to improve the 20 outcomes of health and performance in IR adult women.

Practical application 5: In order of threatening the common co-morbidities (overweight/obesity, high blood pressure, and a low performance), RT using low-loads but looking for a muscle failure in 60 seconds, can be used as therapy for adult women with IR not only for decreasing and improving glucose control, but also to regulate all these secondary symptoms associated with physical inactivity.

Future perspectives 5: Due to RT not only improves glucose control, but also appears to be the most powerful strategy to reduce the number of non-responses when compared with HIT or CT, future studies should include the report of how much pharmacology therapy for decreasing glucose and blood pressure can be reduced in populations with T2DM and HTN diagnosed.

Study 6 [Submitted] (Chapter 7)

The aim of this study was to investigate the effects of a 20-week CT intervention on cardiovascular risk factors such as body composition, blood pressure and lipid profile among adult women with hyperglycaemia. A secondary aim was to report prevalence of non-responders for the different study outcomes

Result 5: Beyond a decrease in fasting glucose (-4 mg/dL on average, $P=0.05$), significant benefits of CT were found for mean values in adiposity (body mass -1.3 kg, $P=0.026$ and WC -4.0 cm, $P<0.0001$) and lipid profile (total cholesterol -12 mg/dL, $P=0.038$; LDL-cholesterol -11 mg/dL, $P=0.022$; HDL-cholesterol +4 mg/dL, $P=0.003$; and triglycerides -25 mg/dL, $P<0.0001$), were these outcomes do not showed changed in control group. Fat mass, lean mass, systolic and diastolic blood pressure do not elicited changes in both CT and CG. At the individual level, the proportion of responders and non-responders, respectively, for a beneficial clinical change in the CT and CG groups were the following: for WC (CT 14% and 86%; CG 0% and 100%), for systolic blood pressure (CT 36% and 14.2%; CG 14% and 7%), for diastolic blood pressure (CT 0% and 0%; CG 7% and 14%), for total- (CT 14% and 29%; CG 7% and 28%), LDL- (CT 21% and 36%; CG 0% and 43%), HDL-cholesterol (CT 14% and 50%; CG 14% and 57%) and triglycerides (CT 21% and 14%; CG 0% and 43%), respectively.

Conclusion 5: In addition to its benefits on glucose homeostasis, a 20-week CT intervention for women with prediabetes can decrease abdominal obesity and improve lipid profile in 'mean' terms, as well as enhance the clinical status of some individuals (*i.e.*, those who are responders) from a 'high' to a 'normal'/'low' cardiovascular risk after training.

Practical application 5: In order of threatening the common comorbidities (overweight/obesity, and hyperlipidaemia-dyslipidaemia/ symptoms at risk of hyperlipidaemia-dyslipidaemia) in subjects with low glucose control such as hyperglycaemic population at risk of T2DM, the promotion of combined exercise modes as CT, including RT using low loads (*i.e.*, $<20\%$ 1RM) followed by ET exercises (endurance walking/running at $<70\%$ maximum heart rate (for 50 and 30 minutes, respectively) are a power strategy to avoid new cardiometabolic risk factor for population at risk of T2DM.

Future perspectives 5: Future studies should include genetic/epigenetic measurements testing in those NR specific proteins related with no HOMA-IR decreases.

PhD Thesis
Cristian Alvarez 2018